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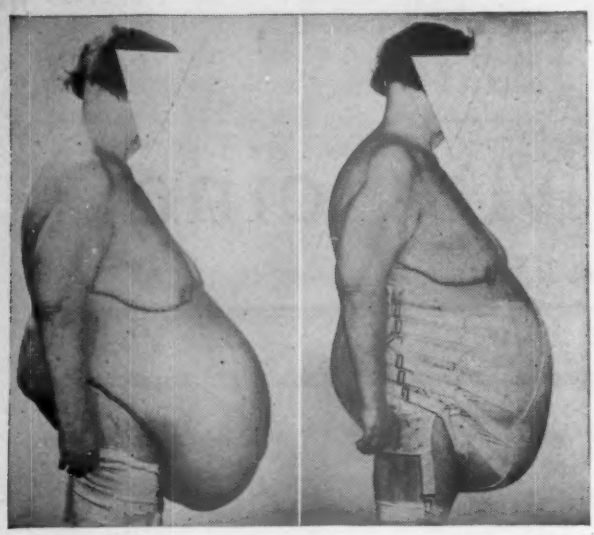

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Volume 238 JUNE 3, 1948 Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§
ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.‖

BOSTON

IT IS the purpose of this paper to record the results of clinical and hematologic studies on 5 children with acute leukemia treated by the intramuscular injection of a synthetic compound, 4-aminopteroylglutamic acid (aminopterin). This substance is an antagonist to folic acid regarding the growth of *Streptococcus faecalis R.*

The occurrence of what he interpreted as an "acceleration phenomenon" in the leukemic process as seen in the marrow and viscera of children with acute leukemia treated by the injection of folic acid conjugates[1] — pteroyltriglutamic acid (teropterin) and pteroyldiglutamic acid (diopterin) — and an experience gained from studies on folic acid deficiency suggested to Farber that folic acid antagonists might be of value in the treatment of patients with acute leukemia.[2] Post-mortem studies of leukemic infiltrates of the bone marrow and viscera in patients treated with folic acid conjugates were regarded by Farber as evidences of an acceleration of the leukemic processes to a degree not encountered in his experience with some 200 post-mortem examinations on children with acute leukemia not so treated. It appeared worth while, therefore, to ascertain if this acceleration phenomenon could be employed to advantage either by radiation or nitrogen mustard therapy after pretreatment with folic acid conjugates or by the administration of antagonists to folic acid.[2] A series of folic acid antagonists was made available by Dr. Y. Subbarow and his colleagues.[3–5]

The objective data sufficient to justify research in the direction of antagonists to folic acid in the treatment of leukemia were obtained from studies on a four-year-old girl with a rapidly progressing acute myelogenous leukemia.[2] Treatment from February 17 to March 24, 1947, with pteroyldiglutamic acid (diopterin), in a dosage of 100 to 300 mg. intramuscularly daily, had no effect upon the hematologic picture. The patient appeared to be moribund. A second bone-marrow biopsy on March 25 verified the diagnosis of myelogenous leukemia. Pteroylaspartic acid, the first antagonist to folic acid to be employed in our studies, was given intramuscularly from March 28 to April 4 in amounts of 40 mg. daily without altering the clinical course. Post-mortem examination on April 4 revealed a markedly hypoplastic bone marrow, with a few immature cells. A change of this magnitude in such a short time has not been encountered in the marrow of leukemic children in our experience.

This observation was followed by clinical, laboratory, and post-mortem studies** on a group of 14 children with acute leukemia treated with pteroylaspartic acid and on 7 treated with methylpteroic acid. The details of these observations will be reported separately.

Sufficient encouragement was obtained from these observations to justify further studies on the effect of more powerful antagonists to folic acid on the course of acute leukemia in children. Since November, 1947, when a sufficiently pure substance became available, to the time of this writing (April 15, 1948) we have made studies on 16 children with acute leukemia to whom the most powerful folic antagonist we have yet encountered, 4-aminopteroylglutamic acid (aminopterin††) was administered by intramuscular injection. Many of these children were moribund at the onset of therapy. Of 16 infants and children with acute leukemia treated with aminopterin 10 showed clinical, hematologic and pathological evidences of improvement of important

*Presented at a meeting of the Division of Laboratories and Research, The Children's Medical Center, Boston, April 8, 1948.

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**These studies were carried out by a group consisting of Sidney Farber, Gilbert G. Lenz, James W. Hawkins, Ernst Eichwald, Robert D. Mercer and E. Converse Peirce, II.

††This compound was first synthesized by the Calco Chemical Division of the American Cyanamid Company.

nature of three months' duration at the time of this report. Six patients did not respond well; 4 of these are now dead, and 2 were unimproved. This paper presents detailed clinical, hematologic and bone-marrow studies in 5 children selected from these 10 who showed evidences of important improvement — the course in the other cases was essentially similar. The patients are selected for the purpose of illustrating some of the problems concerned with the use of aminopterin and because they demonstrate the best results that we have

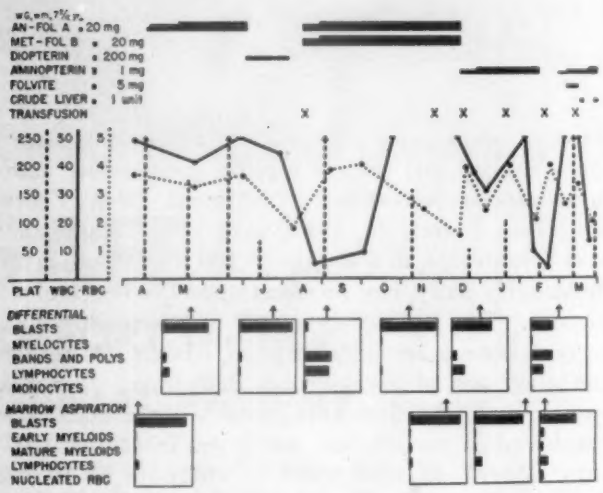


FIGURE 1. *Course of Leukemia in Case 1.*

observed. The toxic effects are stressed in these histories, and the temporary nature of the remissions is emphasized.

CASE REPORTS

CASE 1. W. G., a 7 2/12-year-old boy, entered the hospital for the first time on April 9, 1947, with complaints of joint pain and fever. He had been generally well until 7 weeks before admission, when pain developed in the right knee. There were no associated physical abnormalities, and the pain promptly subsided. Five days later pain recurred in the right elbow, and a low-grade fever was noted. Migratory arthralgia and fever continued until admission.

Physical examination revealed only moderate pallor and slight enlargement of the liver and spleen. The boy appeared well developed and nourished and not particularly ill.

Examination of the blood disclosed a red-cell count of 3,670,000, with a hemoglobin of 10.6 gm., and a white-cell count of 56,000, with 73 per cent blast forms. The platelet count was normal. A bone-marrow biopsy revealed leukemia.

The patient was treated with pteroylaspartic acid beginning on April 16 in doses of 20 to 60 mg. daily while in the hospital, in a convalescent home, where he remained until May 20, and at home, where the injections were given by the family physician. During that time he was active and fairly well, although the white-cell count remained high and the red-cell count and hemoglobin fell slowly.

On July 1 diopterin, in a dosage of 200 mg. by mouth daily, was begun. This therapy was continued for about 1 month, during which the patient steadily became more ill. The liver and spleen enlarged, and he became very anemic. The blast forms in the peripheral blood rose to 94 per cent. Joint pain and fever recurred, and by August 13 he was critically ill, with a temperature reaching 106°F. He was readmitted to the hospital and received several transfusions. Pteroylaspartic acid and methylpteroic acid, in doses of 40 mg. each, were given intramuscularly daily. The patient was discharged after about 2 weeks, and pteroylaspartic acid and methylpteroic acid, in doses of 20 mg. each, were continued in the Tumor Therapy Office. A period of remission ensued, during which the red-cell count and platelets returned to normal levels, the liver and spleen receded in size and the nutrition improved remarkably. He returned to school part time in October and was in quite good condition. The white-cell count had risen to high levels, however, and in November general deterioration began. The liver and spleen enlarged, and he became so anemic that transfusion was necessary by November 24. Only temporary benefit resulted and transfusions were required at about 3-week intervals.

Aminopterin was started on December 16 and given daily, in doses of 0.5 mg. intramuscularly, for six doses. By December 30 the white-cell count had fallen from 60,000 to 19,000. There was moderate improvement in activity and appetite. Thereafter unfavorable weather made daily visits to the clinic impossible, and 1 mg. of aminopterin was given approximately three times weekly for about a month. During that time there was no striking clinical or hematologic improvement, although the patient was not seriously ill.

On February 3 daily injections of 1 mg. of aminopterin were begun. A bone-marrow biopsy and aspiration revealed 85 per cent blast forms, no megakaryocytes and no erythropoiesis. After 10 days of regular therapy the white-cell count had fallen from 78,000 to 5000, but severe stomatitis made cessation of therapy imperative. Within a week without therapy, the stomatitis had healed completely, and the patient had developed a ravenous appetite. The nutrition gradually improved. By February 21 the liver was no longer palpable, and only the tip of the spleen could be felt. Bone-marrow aspiration and biopsy revealed a slight decrease in blast forms and slight erythropoietic activity. The platelets reached normal levels about 1 month after this course of daily therapy. On March 1 the white-cell count began to rise in spite of daily administration of 0.25 mg. of aminopterin, and by March 6 was 75,000. The spleen again enlarged. The dosage of aminopterin was raised to 1 mg. on March 8, and after about 10 days the white-cell count had fallen to 12,000. Slight stomatitis again appeared, and the dosage of aminopterin was reduced to 0.5 mg. daily, with 1 unit of crude liver extract weekly. The white-cell count has remained at a high-normal level, and the spleen is again slowly receding. The stomatitis is still present but is not progressing and does not interfere with ability to eat.

The leukemia in this case progressed slowly during treatment with pteroylaspartic acid and methylpteroic acid, but during a course of diopterin became rapidly worse (Fig. 1). The liver and spleen enlarged, severe anemia developed, and the blast forms in the peripheral blood rose above 90 per cent. The patient appeared critically ill, with a maximum temperature of 106°F. Transfusions and therapy with these two folic acid antagonists were followed by a marked but temporary remission. Irregular therapy with aminopterin has been of no benefit, but on two occasions daily injections have produced good clinical and hematologic remissions. On both occasions, stomatitis has interfered with optimal use of the drug. At the time of writing the patient is in excellent physical condition.

CASE 2. R. P., a 6 4/12-year-old boy, was admitted to the hospital on March 4, 1948, with the chief complaint of increasing pallor. His growth, development and general health had been excellent until about 3 weeks before admission, when tonsillitis had developed. This had subsided promptly, but the patient had become lethargic, and increasing pallor was noted. About 10 days before admission his parents began to notice that he bruised easily.

Physical examination disclosed a well developed and fairly well nourished boy who was very pale and lethargic. Many small ecchymoses were noted over the extremities. The liver edge extended 4 cm. below the costal margin, and the tip of the spleen could be felt at the costal margin. There was slight generalized lymphadenopathy.

Examination of the blood revealed a red-cell count of 1,880,000, with a hemoglobin of 5.65 gm. and platelets of 46,000, and a white-cell count of 4200, with 20 per cent immature or blast forms. A sternal-marrow aspiration revealed 75 per cent blast forms. No megakaryocytes were seen.

Shortly after admission the patient developed a spiking temperature up to 104 or 105°F. daily, and rapidly became more lethargic. Blood cultures revealed no growth. Frequent transfusions raised the red-cell count and hemoglobin to normal levels, but there was no favorable clinical response. The white-cell count fell to 1500. He appeared critically ill. On the 7th hospital day penicillin was started, and the temperature decreased although it continued to reach 101 to 102°F. daily.

On the 8th hospital day, aminopterin (1 mg.) and crude liver extract (1 unit) were given intramuscularly. The white-cell count was 1500. This medication was continued daily, and the patient rapidly became more alert and active. The white-cell count remained near 2000. He was discharged moderately improved on March 15. After discharge he was seen 6 times weekly in the Tumor Therapy Clinic and 1 mg. of aminopterin and 1 unit of crude liver extract were given at each visit. Rapid improvement in appetite and activity continued. A second sternal-marrow biopsy and aspiration after one week of therapy revealed a 25 per cent decrease in blast forms and an increase in more mature leukocytes and megakaryocytes. By March 25 the white-cell count had reached 5000, with 34 per cent neutrophils, 63 per cent lymphocytes and 2 per cent blast forms. His activity and appetite were normal and easy bruising was no longer a complaint. At about that time he developed minor

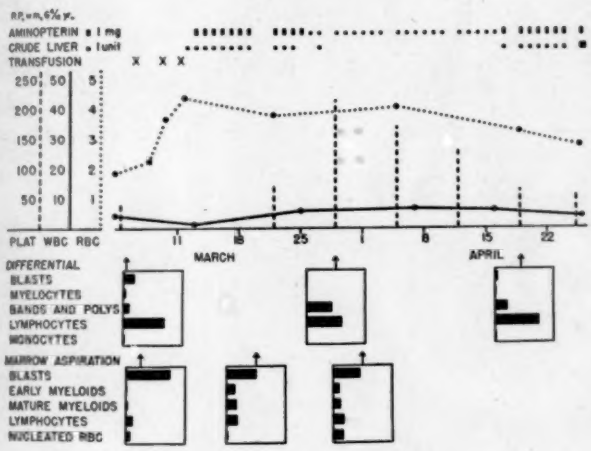


FIGURE 2. *Course of Leukemia in Case 2.*

lesions of the oral mucosa. The dosage of aminopterin was reduced to 0.5 mg., and the liver extract was given once weekly. Steady improvement has continued. The liver and spleen are no longer palpable. The patient is active in outdoor games, and his endurance is good. On March 31 he returned to school, where his teacher noted marked improvement in his appearance and interest. Sternal-marrow aspiration on April 1 revealed a slight further reduction in blast forms, a moderate increase in megakaryocytes and a marked increase in erythropoiesis. He continues on daily injections of 0.5 mg. of aminopterin with liver extract once weekly.

This patient had rapid progression of leukemia until one month after the onset, when he appeared critically ill. After three weeks of daily aminopterin therapy his activity and appearance have returned to normal and he is in school part time. The red-cell count and hemoglobin are still high, and the white-cell count is within normal limits. Immature cells or blast forms have disappeared from the peripheral blood, and the bone marrow shows a moderate shift toward maturity of leukocytes, with an increase of erythrocyte precursors and megakaryocytes. The course is demonstrated in Figure 2.

CASE 3. G.J., a 3 8/12-year-old boy, was admitted to the hospital on November 2, 1947 — 5 days after the onset of an acute illness with sore throat and fever.

The past history, birth and developmental history were not remarkable.

Physical examination disclosed a critically ill patient with an acute follicular tonsillitis and enlarged tender cer-

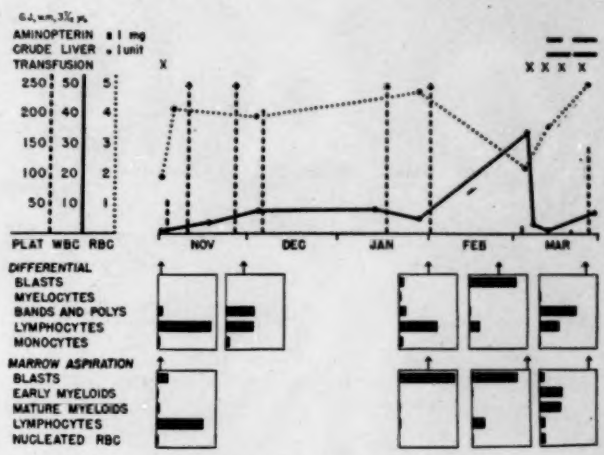


FIGURE 3. *Course of Leukemia in Case 3.*

vical lymph nodes. There was no generalized adenopathy and no hepatomegaly or splenomegaly. A blood culture was positive for beta-hemolytic streptococcus.

Examination of the peripheral blood showed a red-cell count of 1,900,000, a white-cell count of 480 and a platelet count of 123,000. Bone-marrow aspiration showed 16.4 per cent blast forms, 3.2 per cent mature polymorphonuclear leukocytes, 76.2 per cent lymphocytes and 1.6 per cent erythroid elements. On the basis of the bone-marrow aspiration a diagnosis of leukemia was made. The bacteremia was treated with penicillin and streptomycin.

After recovery from the infection the patient went into a complete clinical and hematologic remission for about 2 months. The course is demonstrated in Figure 3. At that time bilateral acute otitis media developed. Two weeks later the total nucleated count of the sternal bone marrow was 910,000 (normal 200,000 to 250,000), with 96 per cent blast forms (Fig. 4*A*). By February 26, 1948, the white-cell count was 17,250, with 80 per cent blast forms, the spleen extended to the umbilicus, petechiae began to appear, and it was obvious that the child was entering a rapidly progressive phase of the leukemia.

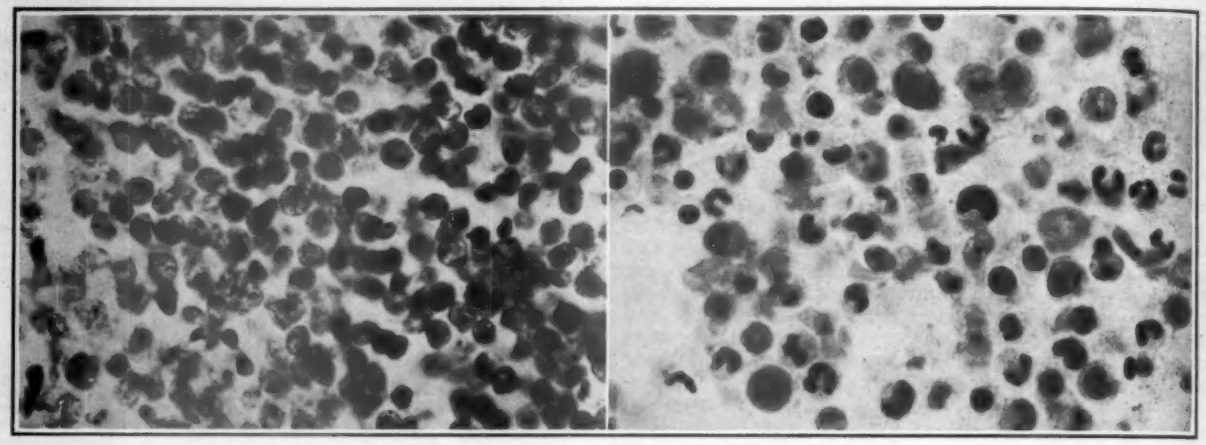
He was readmitted to the hospital on March 6. He appeared chronically ill, with pallor, petechiae, moderate generalized lymphadenopathy and marked hepatomegaly and splenomegaly. The white-cell count, which was 30,400, with 86 per cent blast forms, on admission, fell rapidly to 900 by March 12, and the patient appeared moribund. Blood cultures were negative.

Aminopterin was started on March 13 in doses of 0.5 mg. and given for 5 consecutive days. Crude liver extract, in a dosage of 1 unit daily, was given in the same syringe. At

the end of that time there was no noticeable clinical improvement, but the white-cell count, which was still 900, contained only 5 per cent blast forms. A sternal-marrow smear made at the end of this short period of therapy and compared to one just before therapy was started showed a shift to the right, with some reduction in blast forms and an increase in more mature forms of granulocytes, as well as a slight increase in erythroid elements. Aminopterin was discontinued until it became apparent that the leukopenia was not increasing.

After 4 days without treatment 0.5 mg. of aminopterin daily, with 1 unit of crude liver extract, was given once more. The white-cell count increased gradually, and blast forms disappeared from the peripheral blood. The child began to show clinical improvement, his appetite became better, and the liver and spleen became scarcely palpable. The petechiae and generalized adenopathy disappeared.

At the present writing there is a partial contracture of the left leg, probably resulting from leukemic infiltrations about the knee joint and in the gastrocnemius muscle. The tip of the spleen is still palpable. Otherwise the child is normal on physical examination. The white-cell count is 6700, with a normal differential. The platelet count is 152,000. Aspiration of the sternal marrow on March 29 revealed 8 per cent blast forms, with an increase in more mature granulocytes, erythrocyte precursors and megakaryocytes (Fig. 4*B*).



A B

FIGURE 4. *Photomicrographs of the Sternal Bone Marrow in Case 3, Showing Giemsa-Stained Section on January 29,* (A) *and April 3* (B), *1948 (x1000).*

Note that the microscopical field is composed mainly of blast forms characteristic of leukemia (cell type undetermined) in the early section (A) *and that a marked shift to mature cell forms, particularly of the polymorphonuclear series, with no leukemic cells, had occurred on the later examination* (B).

This child with acute leukemia had a remission of about two months' duration after a bacteremia. At the time aminopterin was started he was in a rapidly progressive phase of the leukemia and appeared moribund. After five days of therapy there was marked improvement in the peripheral-blood and sternal-marrow picture. He has continued to demonstrate rapid and remarkable clinical improvement. Eighteen days after therapy was started the sternal-marrow aspiration showed only a slight shift toward immaturity of the myeloid elements and a moderate reduction of lymphocytes and erythroid elements. The peripheral blood at present shows slight thrombocytopenia, with a white-cell count of 8000 and a differential count that is essentially normal except for a large number of band forms.

CASE 4. C. C., a 2 1/12-year-old girl, was admitted to the hospital on August 22, 1947. Six weeks previously her father had noticed lumps about the head and neck. Two weeks previously her family physician had made a diagnosis of leukemia on the basis of a peripheral blood smear.

Physical examination revealed a pale girl, with ecchymotic areas over the lower extremities. There was marked generalized adenopathy, particularly about the parotid region, and the liver edge and tip of the spleen extended down to the iliac crests.

Examination of the blood disclosed a white-cell count of 75,000, with 80 per cent blast forms. The platelet count was 54,000. The patient was discharged and given x-ray therapy to the parotid region in the outpatient department. A total of 600 r was given from September 4 to September 8. The white-cell count, which was 94,000 on September 4, had dropped to 5000 by September 11.

The patient was readmitted on September 27. She was much worse, with a poor appetite, marked pallor and massive adenopathy. The white-cell count was 1000, with 30 per cent blast forms. Several transfusions before discharge produced only slight improvement.

The third admission, on November 6, followed a generalized convulsion. The patient was comatose, with a temperature of 103.6°F.

Physical examination was essentially unchanged except that the kidneys were definitely enlarged and easily palpable. There was no positive evidence of infection. A transfusion and penicillin were given, and the patient was discharged in fair condition.

The fourth and last admission was on December 2, when there was a temperature of 105°F. There was a severe stomatitis and pharyngitis, with extensive exudation. The left ear was inflamed but not suppurating. Bronchopneumonia was present on the left. A lumbar puncture showed evidence of subarachnoid hemorrhage. A blood culture was positive for *Staphylococcus aureus*, coagulase positive.

For the first 6 hospital days the patient ran a septic temperature ranging between 105 and 103°F. She was given penicillin and sulfadiazine, as well as repeated blood transfusions, throughout the hospital stay. At this admission she was seen for the first time by the Tumor Clinic and received 20 mg. of teropterin per day for eighteen doses, from December 3 through December 20.

On several occasions the patient appeared moribund but on about the 7th hospital day she began to improve and continued to improve until the time of her discharge. The white-cell count, which had dropped to 650 on the 4th hospital day, rose to 6400 on the day before discharge. The differential count included 68 per cent neutrophils, 24 per

cent lymphocytes and 8 per cent monocytes. There were no blast forms.

After this severe infection there was a remission in the clinical and hematologic condition. During that time the patient was given an occasional dose of teropterin to a total of 140 mg. By January 13 small lymph nodes over the scalp, parotid and cervical regions had begun to develop. These rapidly increased, and by January 19 there was massive generalized adenopathy. The peripheral blood and bone marrow continued at values approaching normal. There were only occasional to 5 per cent blast forms in the peripheral blood, with a normal total white-cell count, and 8.4 per cent blast forms in the bone marrow, with a slight depression of mature forms and a moderate depression of erythroid forms. On January 20 aminopterin was started in doses of 1 mg. daily with 20 mg. of teropterin daily. This was given on twenty-six clinic visits from January 20 to February 21. Four days after treatment had been started there was a marked decrease in the size of all the lymph nodes. In 2 weeks the patient was normal on physical examination. Her appetite became very good, her disposition happy, and she began to play and run about like a normal child. Her parents stated that she was better than she had been before she became sick for the first time. Since treatment was stopped she has continued to do well. She has been without treatment since February 21 and at present is completely normal on physical examination. The total white-cell count is 9000, with an occasional blast form. The platelet count is 256,000, the red-cell count 4,600,000 and the hemoglobin 14.8 gm.

This child is known to have had acute leukemia since early in August, 1947. Her course was rapidly and progressively downhill until December, when she had a fulminating generalized infection with bacteremia. After this she had clinical and hematologic evidence of remission. In the middle of January a relapse was taking place, as evidenced by massive generalized adenopathy although the blood and bone-marrow picture remained the same. After aminopterin therapy the adenopathy disappeared. The patient has remained clinically well for forty-three days without treatment and shows an essentially normal hematologic picture at the time of writing. The course is shown in Figure 5. At the end of forty-seven days without treatment a few nodules appeared beneath the scalp and in the subcutaneous tissue over the face. It is probable that these represented leukemic deposits, although at the time of their appearance the peripheral blood was still essentially normal. Because of this finding the treatment has been reinstituted.

Case 5. R. S., a 2 2/12-year-old boy, was admitted to the hospital on August 26, 1947, with the chief complaint of increasing pallor. He was one of identical twins, and his birth, growth and development, and general health had been unremarkable. About 10 days before admission he had developed a low-grade fever, soon followed by increasing pallor, lethargy, anorexia and intermittent vomiting.

Physical examination showed a fairly well developed and well nourished and only moderately ill boy. He was very pale. There was generalized enlargement of the lymph nodes and moderate hepatomegaly and splenomegaly. X-ray study showed marked infiltration of the long bones. The hemoglobin was 5.5 gm., and the white-cell count 12,400, with 41 per cent immature or blast forms.

During 2 weeks in the hospital the patient received transfusions, which restored the hemoglobin to normal levels. After discharge he was seen in the Tumor Therapy Clinic daily except Sunday and on each visit received 20 mg. of pteroylaspartic acid intramuscularly. He continued on this regime for about 2 months, during which the disease progressed slowly but steadily. He became less alert and less active. He developed a limp. There was gradual weight loss, and the liver and spleen continued to enlarge. The leukocytes remained at normal levels but the percentage of blast forms increased. The red-cell count and hemoglobin slowly fell, until on November 6 it was necessary to admit him to the hospital for transfusion. At that time a small pathologic fracture was noted in the left tibia. After discharge he was seen in the Tumor Therapy Office three times weekly and on each visit received 40 mg. of pteroylaspartic acid intramuscularly. Late in November there was a definite acceleration in the progress of the disease. The white-cell count began to rise, and the platelets fell. The patient began to bruise easily and had occasional slight oozing from the gums. He developed moderate exophthalmos. He refused to walk. Hospitalization was necessary twice in the

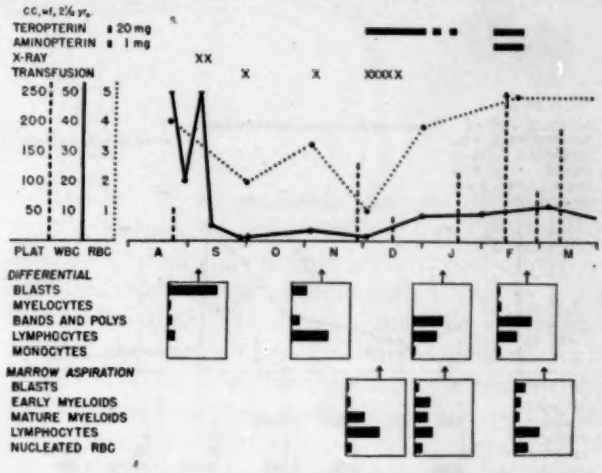


Figure 5. *Course of Leukemia in Case 4.*

early weeks of December for treatment of arthritis and upper respiratory infection. Sternal-marrow aspiration at that time revealed 40 per cent blast forms and little erythropoiesis. By the end of December the patient appeared moribund. He had marked generalized adenopathy, marked hepatomegaly and a spleen whose tip extended into the pelvis. There was moderate dyspnea and stridor, pallor, marked wasting and exophthalmos. There were many ecchymoses, and oozing occurred at the gingival margins.

Aminopterin therapy was begun on December 28. On each of 3 successive days the patient received 1.0 mg. of the drug intramuscularly. During that time the white-cell count began to fall rapidly from the pretreatment level of 60,000. By December 31 the count was 9000, and respiratory difficulty was even more marked. He was admitted to the hospital, aminopterin was discontinued, and a transfusion was given. He was discharged on January 3, 1948, slightly improved, but with the white-cell count only 2700. After discharge he was again followed in the Tumor Therapy Clinic. By January 13 marked clinical improvement had become apparent. The patient was walking for the first time in 2 months, and respiratory difficulty had disappeared. His appetite was ravenous. There was no more bleeding. "His clothes became loose about the abdomen." On January 27 the white-cell count reached 5000, and 0.5 mg. of aminopterin was started and given three times weekly. Gradual improvement continued, but a white-cell count of about 3000 persisted. In the middle of February, teropterin in 10-mg. amounts was given with each dose of aminopterin for five doses. Early in March a rise in the hemoglobin and red-cell count began. Since then folic acid for a time and lately crude liver extract have been used in conjunction with aminopterin. There had been steady clinical and hematologic improvement so that at the time of writing, activity, alertness and nutrition are equal to or better than those of the well twin. The liver and spleen have decreased in size, so that they are barely palpable beneath the costal margins. Exophthalmos has disappeared. The red-cell and white-cell

count, differential counts and platelets are within normal limits. The sternal marrow, examined by biopsy, is normally cellular, and the differential count is normal. Erythropoiesis is active, and megakaryocytes are present in normal number.

This boy exhibited slow but regular progression of leukemia from the time of diagnosis in August, 1947, until December, when he became rapidly worse. By January, 1948, he appeared moribund. After three daily doses of 1 mg. each of aminopterin there was a rapid fall in the white-cell count, followed in about ten days by remarkable clinical improvement. On maintenance therapy there has been continued improvement until at present the

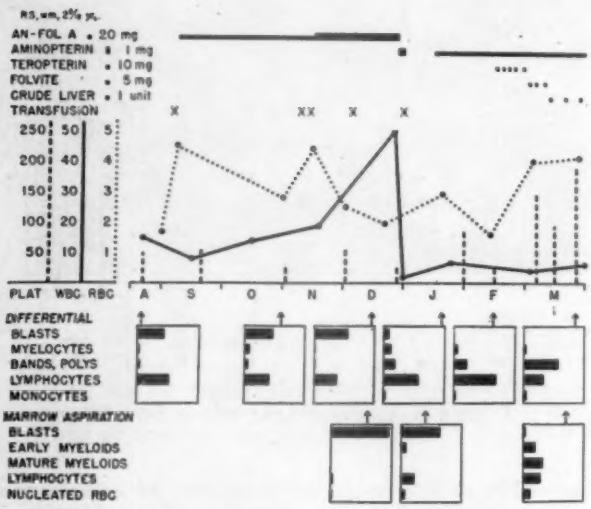


FIGURE 6. *Course of Leukemia in Case 5.*

patient is clinically well and all the laboratory data are within normal limits. The course is demonstrated in Figure 6.

DISCUSSION

Clinical, hematologic and histologic details are given concerning 5 children with acute undifferentiated leukemia treated with aminopterin. These patients were selected from a group of 10 who responded favorably to the use of this substance. The 10 were members of a group of 16 children with acute leukemia — 6 did not respond well, and of these, 4 are now dead. The observations on these patients show that the aminopterin has a marked effect upon the leukemic bone marrow and upon the immature cells in the peripheral blood, and judging from the disappearance of enlargement of the spleen, liver and lymph nodes, when those organs were enlarged, very probably on leukemic deposits in the viscera as well.

Under treatment with aminopterin the white-cell count tended to return to a normal level. This occurred in patients in whom the count was initially high and also in those in whom there was marked leukopenia at the onset of the therapy. The percentage of immature cells fell, and the blast forms decreased markedly and in some cases disappeared from the peripheral blood. The relative percentages of mature leukocytes tended to approach normal values in the peripheral blood. The peripheral-blood changes included improvement approaching the normal in the value of hemoglobin, red-cell count and platelets. Studies of the bone marrow showed changes that varied from a decrease in number to a disappearance of the leukemic cells and variation from hypoplasia to almost normal pattern. Toxic effects included stomatitis, with early ulceration. In an attempt to prevent this complication crude liver extract was employed, as were folic acid and folic acid conjugates.

This report describes only temporary remissions produced by the injection of aminopterin in children with acute leukemia. It is impossible to state whether the substance will be of value for a longer period than that covered by these studies. The toxic effects may make continued use of the drug impossible. One patient (Case 4) had been without treatment for forty-three days after having had a satisfactory remission. During this time the peripheral blood and the sternal bone marrow became essentially normal. At the end of forty-seven days without treatment a few nodules appeared beneath the scalp and in the subcutaneous tissue over the face. It is probable that these represent leukemic deposits, although at the time of their appearance the peripheral blood was still essentially normal. Because of this finding the treatment has been reinstituted. After ten days of aminopterin treatment, the nodules have disappeared once more.

These studies justify a search for other antagonists to folic acid that are less toxic than aminopterin and may be even more powerful.

SUMMARY

Clinical, hematologic and histologic details of 5 patients with acute leukemia treated with aminopterin, selected from a group of 16 patients so treated, form the basis of this paper. It is again emphasized that these remissions are temporary in character and that the substance is toxic and may be productive of even greater disturbances than have been encountered so far in our studies. No evidence has been mentioned in this report that would jus-

tify the suggestion of the term "cure" of acute leukemia in children. A promising direction for further research concerning the nature and treatment of acute leukemia in children appears to have been established by the observations reported.

Acknowledgment is made to Dr. Y. Subbarow and his colleagues in the Research Division of the Lederle Laboratories (American Cyanamid Company) and their associates of the Calco Chemical Division, who are responsible for the chemical research that made possible these studies on children.

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SARCOMA OF THE UTERUS*

A Report of Eighteen Cases

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ALTHOUGH sarcomas of the uterus are rare in comparison with the carcinomas of that organ, certain features of their histogenesis, pathology and clinical course make them an interesting group. Two recent cases, a sarcoma botroides and a late metastasizing leiomyosarcoma, prompted a review of the 18 cases of sarcoma of the uterus seen at the Rhode Island Hospital in the past eighteen years. Special attention has been paid to the pathology of these cases with a view to determining their probable origins and the relation of cytologic characteristics to prognosis. Observations have also been made on the clinical characteristics of the disease, with particular reference to radiation therapy. Four cases are of sufficient interest to be reported in some detail.

A brief review of the literature serves to orient one concerning the types of tumors encountered and their incidence. In 1863 Virchow[1] pointed out that sarcomas may arise both in the smooth muscle of the uterus and in the stromal cells of its mucosa. Geisler[2] noted that sarcoma constituted 2 per cent of uterine cancers, Novak and Anderson[3] found 4.5 per cent, and others a similar or slightly higher incidence. Piquand,[4] in a collective study, reported 68 cases of sarcoma of the cervix as compared with 325 of the body. Others found a much lower incidence of tumors in the cervix (Gessner[5] and Meyer[6]).

Nearly all authors report a preponderance of leiomyosarcomas over other forms of uterine sarcomas. Leiomyosarcomas may be of a very low grade of malignancy, some being classified as recurrent fibroids. Others are extremely anaplastic, widespread and rapidly fatal. Various gradations between the two extremes are to be found. Grossly, the tumors may be nodular or may grow diffusely. Polypoid projections into the endometrial cavity are not uncommon.

Stromal or mucosal-cell cancers of the endometrium make up the other large group of uterine sarcomas. These are usually characterized by round cells rather than the spindle cells found in typical leiomyosarcoma. The group may be enlarged to include the various types of mixed tumors, which, in spite of their pleomorphism, presumably arise from stromal cells or their anlage. A rather confusing nomenclature has arisen for them, but, for the purposes of this paper, the following terminology is used. Mixed mesodermal tumors are those containing more than one type of tissue of mesodermal origin. Cartilage, striated muscle and myxomatous elements are most frequently encountered, but many other types of tissue have been noted. The term carcinosarcoma is used to designate tumors containing elements of connective-tissue origin and epithelium. It cannot be argued that the presence of epithelial cells sets the carcinosarcomas apart from other mixed tumors, but the term is descriptive and gives some indication of cell structure. From a careful study of the histology of the cases reported in this paper it seems likely that a large proportion of stromal-cell tumors show a mixed histology. Multiple microscopical sections may reveal small islands of cartilage or bizarre epithelial elements that are overlooked in routine observation. Thus, it was possible to reclassify several of the tumors reported below.

Two other types of rare sarcoma should be mentioned: hemangiosarcoma and sarcoma botroides. The latter is the grapelike tumor most often found in the cervical portio of infants, but also seen in adults. It presents a mixed histology, which includes epithelium, myxomatous tissue, striated muscle and, at times, a variety of other elements. This tumor is extremely malignant.

Any series of these tumors includes some that are too anaplastic to be classified. Certain others are characterized only by round cells and large num-

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bers of giant cells (Fig. 1 and 2). Inasmuch as both leiomyosarcomas and stromal-cell tumors tend to form giant cells these tumors cannot always be accurately pigeonholed. Novak and Anderson[3] point out that the giant cells are often evidence of degeneration of the tumor and that a diagnosis can frequently be made by a careful search for areas with few giant cells.

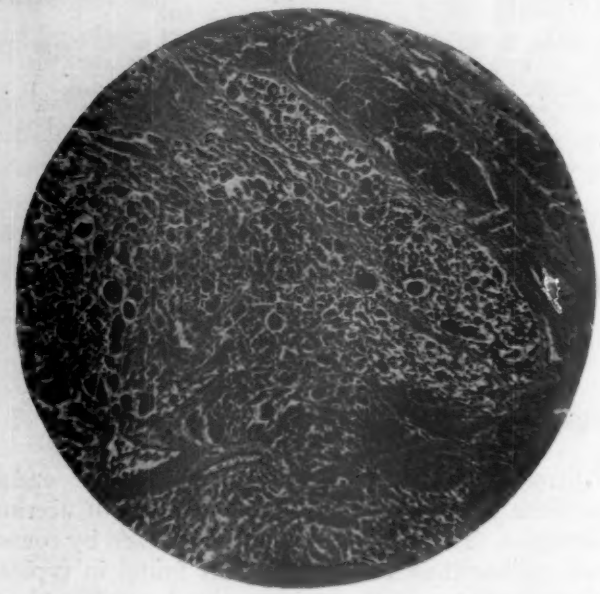

FIGURE 1. *Advancing Edge of a Predominantly Giant-Cell Tumor (Case 16).*

The varied histology of the mixed types of tumors calls for some consideration of their histogenesis. It will be recalled that both myometrial and endometrial elements of the uterus are derived from the müllerian ducts, which, in turn, are outpouchings of the wolffian ducts, the last being of mesodermal origin. In the uterus of the 80-mm. embryo (Prentiss and Arey[7]) myometrial and endometrial layers can be distinguished. It will be seen, therefore, that a müllerian-duct cell can give rise to smooth muscle, endometrial stroma or epithelium. This fact may well account for the pleomorphism of some of the tumors encountered.

From 1929 through February, 1947, 18 patients with sarcomas of the uterus have been treated at the Rhode Island Hospital. These can be classified as follows: leiomyosarcoma, 7 cases; mixed mesodermal sarcoma, 4 cases; carcinosarcoma, 3 cases; giant-cell (probably stromal-cell) sarcoma, 2 cases; stromal-cell sarcoma, 1 case; and sarcoma botroides, 1 case.

FIGURE 2. *A Few Areas Suggesting Stromal-Cell Origin from the Same Tumor As That Shown in Figure 1.*

TABLE 1. *Results of Treatment in Patients with Leiomyosarcoma.*

CASE NO.	AGE OF PATIENT	TREATMENT	PERIOD OF SURVIVAL	REMARKS
	yr.		*mo.*	
1	90	Panhysterectomy and bilateral salpingo-oophorectomy	3	Gross tumor not completely removed; patient died of leiomyosarcoma.
2	65	Panhysterectomy and bilateral salpingo-oophorectomy	5	No recurrence of tumor; patient died of chronic myocarditis.
3	48	Panhysterectomy and bilateral salpingo-oophorectomy	66	Recurrence after 4½ years; patient living.
4*	54	Panhysterectomy and bilateral salpingo-oophorectomy; 2400 r postoperatively.	8	Gross tumor not completely removed; patient died of leiomyosarcoma.
5*	20	Supracervical hysterectomy	48	No recurrence; patient living.
6	53	Supracervical hysterectomy and unilateral salpingo-oophorectomy; 2150 r postoperatively.	6	Gross tumor not completely removed; patient died of leiomyosarcoma.
7*	43	Panhysterectomy and bilateral salpingo-oophorectomy.	12	No recurrence; patient living.

*These patients showed few mitoses, indicating good prognosis.

The results of treatment in the patients with leiomyosarcoma have not been encouraging (Table 1). In 3 cases gross tumor had to be left behind at the time of operation, and all these patients were

dead within eight months. In the other cases, viewed as possible cures at the time of operation, 1 patient died in five months without evidence of recurrence, 1 developed a distant metastasis after four and a half years, and 2 are living and well one and four years, respectively, after operation.

Panhysterectomy with bilateral salpingo-oophorectomy is considered to be the treatment of choice. In Case 5 it was not done because the diagnosis of leiomyosarcoma was not made at the time of operation even though a curettage was performed. In Case 6 the cervix and surrounding tissues were intimately involved in the tumor, and the cervix was therefore left behind.

Two patients received x-ray therapy postoperatively. One (Case 4) was noted at operation to have metastatic involvement of the iliac and low aortic lymph nodes. During the first three weeks postoperatively these areas were treated with 2400 r of x-ray therapy given to each of two portals. The patient died in eight months without evidence of improvement due to radiation. In Case 6 tumor

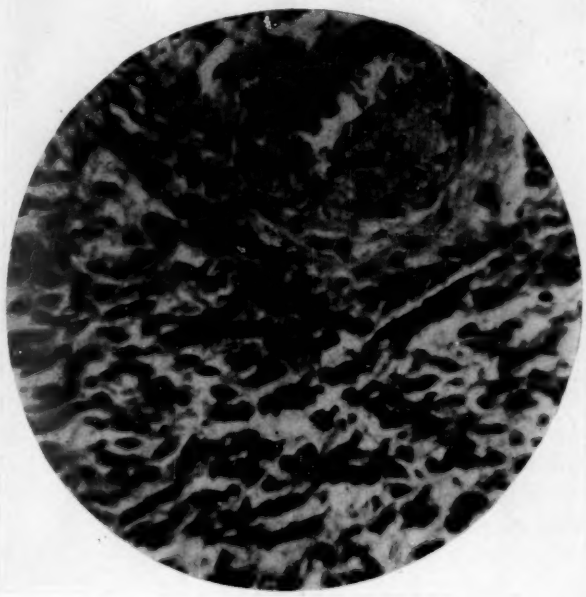

FIGURE 3. *Leiomyosarcoma in Case 7.*
This shows a relatively benign growth resembling a very cellular fibroid but lacking a capsule as it encroaches on the blood vessel above.

left in the region of the cervix did not respond to 2150 r given within three weeks of operation. This patient also died of the disease in six months.

On the whole these patients were operated on soon after symptoms appeared. Four had had symptoms for less than three months, 1 for three and 1 for four months, and 1 for two years.

Bleeding, pain and abdominal mass were the most frequent complaints, the major symptoms being as follows: bleeding, 2 cases; mass, 2 cases; pain, 2 cases; and bleeding, pain and mass, 1 case.

In spite of reasonably prompt surgery after the onset of symptoms most of the patients had advanced disease when explored. One had polypoid masses filling the entire endometrial cavity, with extension to an ovary. Three others had large masses, 10 cm. or over in diameter, with extension outside the body of the uterus. The masses in the remaining 3 cases were 3, 4 and 5 cm. in diameter. Of these patients 2 (Cases 5 and 7) are living and well after one and four years, and another (Case 2) died of other disease in five months. This indicates that early lesions have a rather favorable prognosis.

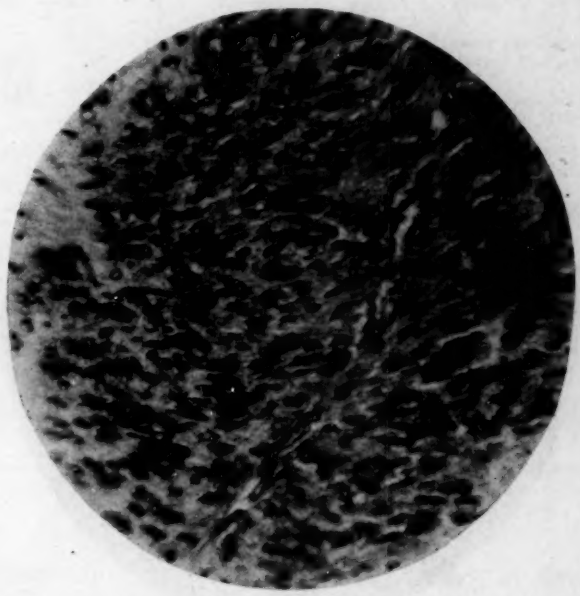

FIGURE 4. *Leiomyosarcoma, with Slight Variation in Cell Morphology (Case 3).*

Evans,[8] in a painstaking study, was able to show that the prognosis of leiomyosarcoma bears a relation to the number of mitotic figures in a given lesion. He divided his 72 cases into three groups according to the number of mitoses and found excellent results in those with no or very few mitoses per cubic millimeter. In the series reported in this paper there were 3 such cases. One patient (Case 4) had a tumor that had too great local extension for complete removal when she was first seen. Two others (Cases 5 and 7), as mentioned above, had small tumors (Fig. 3) and are living after one and four years. Presumably, tumors with few mitoses grow slowly and are discovered in many cases when still of small size.

It was also found that some of the larger tumors presented a varied histology, certain areas being much more anaplastic and widely growing than others. This suggests that sometimes areas of low-grade malignancy give rise to more rapidly growing tumor tissue with numerous mitoses (Fig. 4 and 5).

None of these tumors seemed to arise from the cervix. Only one of them was found associated with fibroids. This supports the views of Evans[8] and others, as opposed to the still popular concept that leiomyosarcoma arises from preexisting leiomyoma. That such an occurrence is possible is not doubted. Indeed, Novak and Anderson[3] presented a photomicrograph of a leiomyosarcoma within a leiomyoma. It seems likely, however, that most of the tumors are malignant from their inception.

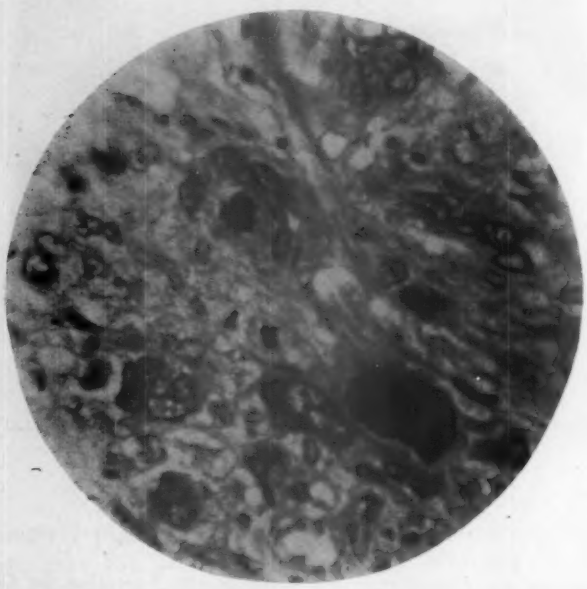

FIGURE 5. *Highly Malignant Area, with Bizarre Mitoses from the Tumor Shown in Figure 4.*

The following case is presented in detail because of interesting points in the histology of the tumor, and the course of the disease.

CASE 3. E. R., a 48-year-old woman, was admitted to the hospital on October 16, 1941, with a complaint of a low abdominal tumor of 4 months' duration.

Physical examination was not remarkable except for a mass rising out of the pelvis to the umbilicus. A preoperative diagnosis of leiomyoma of the uterus was made, and a supravaginal hysterectomy and bilateral salpingo-oophorectomy were done on October 20. The immediate postoperative course was not remarkable. A pathological diagnosis of leiomyosarcoma of the uterus extending into the left parametrium was made.

In May, 1942, the patient noted a lump in the neck, and a substernal thyroid gland containing multiple adenomas was removed.

When seen on March 11, 1946, the patient had no complaints. On her next visit, 1 year later, she stated that she had been having increasing pain in the left shoulder since the last check-up. There was a tender swelling in the region of the head of the humerus, and x-ray examination showed a cystic mass, with a pathologic fracture, expanding the upper end of the humerus (Fig. 6). The roentgenogram was consistent with a benign giant-cell tumor of bone except that the cortex was broken in places. Metastasis from cancer in the thyroid gland was suspected inasmuch as it is well known that a malignant lesion may be missed in the pathological study of apparently benign adenomas of the thyroid gland. On March 24, 1947, an aspiration biopsy of the bone tumor was performed, and a large specimen of leiomyosarcoma obtained. In the absence of other demonstrable metastasis a shoulder-girdle amputation was advised. This operation is understood to have been performed elsewhere. The patient is still living at the present writing.

This case presents several interesting aspects. The tumor did not recur clinically for four and a half years. Metastasis to bone is very rare in these tumors. Histologically, the original tumor presented many striking characteristics. Most of it was of a low grade of malignancy without mitoses (Fig. 4). Other regions presented a chaotic appearance, with numerous giant cells and vacuolated cytoplasm. This finding alone is of little note, but the presence in certain areas of numerous bizarre mitoses in association with giant cells (Fig. 5) forecasts a poor prognosis according to Evans.[8] This was subsequently borne out.

FIGURE 6. *Metastatic Leiomyosarcoma of the Humerus Simulating Benign Giant-Cell Tumor of Bone (Case 3).*
This tumor appeared four and a half years after removal of the primary growth.

Table 2 presents the pertinent data in 11 cases of stromal-cell tumors or mixed tumors of various types. Of these cases the last (Case 18) is considered separately. Of the other 10, the tumor was inoperable in 1 because of widespread disease. Four more could be treated only by exploration or partial removal of the tumor, and 1 had an inadequate follow-up study. Of the remaining 4 patients, who

were regarded as possibly cured at the time of operation, 2 had recurrence in eleven and eighteen months, and 2 are living without positive evidence of recurrence after five and thirteen years. One of these eradicated by radiation. The patient is alive and well five years postoperatively.

Another patient (Case 14) had a much more extensive carcinosarcoma for which she received pre-

TABLE 2. *Pertinent Data in Patients with Sarcoma of Various Types.*

Case No.	Age	Pathological Classification of Tumor	Treatment	Period of Survival	Remarks
	yr.				
8	63	Mixed mesodermal sarcoma with striated muscle	Panhysterectomy and bilateral salpingo-oophorectomy	—	Patient followed for only 2 months
9	56	Mixed mesodermal sarcoma with cartilage	Supravaginal hysterectomy	13 yr.	No recurrence; patient still living.
10	68	Mixed mesodermal sarcoma with cartilage	Curettage and radium	11 mo.	Tumor inoperable; gross tumor not completely removed; patient stated to have died of carcinoma of stomach.*
11	60	Mixed mesodermal sarcoma with myxomatous tissue	Exploratory laparotomy and biopsy	3 days	Gross tumor not completely removed; patient died of sarcoma and bronchopneumonia.
12	70	Carcinosarcoma	Radium preoperatively; panhysterectomy and bilateral salpingo-oophorectomy.	5 yr.	No recurrence; enlarged liver observed 1 yr. after operation (possible metastases); patient living.
13	56	Carcinosarcoma	Wertheim hysterectomy and x-ray therapy for recurrence	38 mo.	Recurrence after 18 mo.; patient died of sarcoma.
14	72	Carcinosarcoma with striated muscle	X-ray therapy preoperatively; panhysterectomy and bilateral salpingo-oophorectomy.	3 mo.	No recurrence; patient living.
15	66	Stromal-cell sarcoma	Panhysterectomy and unilateral salpingo-oophorectomy; x-ray therapy (2412 r) postoperatively.	3 mo.	Gross tumor not completely removed; patient died of sarcoma.
16	51	Giant-cell sarcoma†	Radium preoperatively; exploratory laparotomy and biopsy.	5 mo.	Gross tumor not completely removed; patient died of sarcoma.
17	58	Giant-cell sarcoma†	Panhysterectomy and bilateral salpingo-oophorectomy	22 mo.	Recurrence after 11 mo.; patient died of sarcoma.
18	½	Sarcoma botroides	Hysterotomy	4 mo.	No recurrence; patient living.

*Cause of death given in city report; death may have been due to sarcoma.
†Tumor probably of stromal-cell origin.

(Case 9) had a mixed mesodermal tumor containing cartilage and lining the endometrial cavity to a depth of 2 cm. The other (Case 12) had a carcinosarcoma with a very small base in one horn of the uterus.

All these tumors lined or projected into the endometrial cavity. Some of the smaller ones assumed polypoid characteristics. Unfortunately the series is too small for any conclusions to be drawn regarding the relation of gross or microscopical findings to prognosis. It can be determined, however, that the chief cause of the low survival rate is the silent nature of many of the tumors. One of the largest, reaching to the umbilicus, caused only a distended abdomen for three days prior to hospital entry, and several other patients had equally large tumors after less than two months of symptoms.

Two patients who received preoperative radiation furnish concrete evidence of the effects of this form of therapy on the tumors. The first (Case 12), a seventy-year-old woman, was curetted, and 2450 mg. hours of radium was applied within the uterus three weeks prior to hysterectomy. The operative specimen contained three free portions of necrotic tissue, which had apparently been attached to a ragged area in one horn of the uterus. This region also presented much necrotic material. No viable tumor cells were visible in any of the routine sections. It seems fairly obvious that this was a pedunculated sarcoma and that it had been completely

operatively a total of 2190 r through each of three portals. This was given in two courses during the seven weeks before operation. In the specimen the

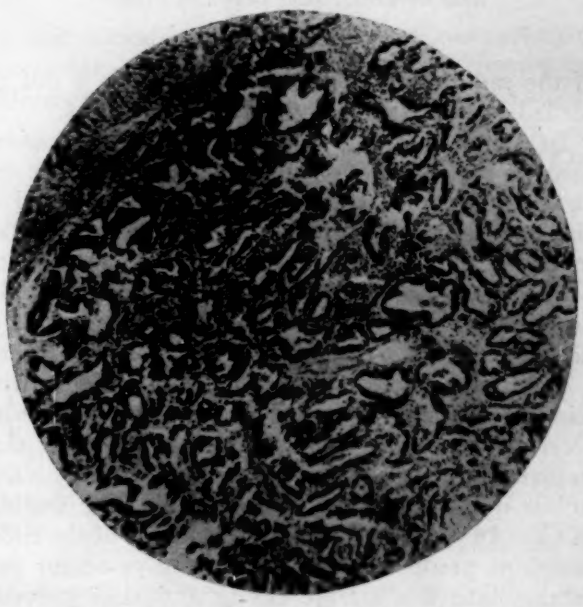

FIGURE 7. *Carcinosarcoma (Case 13), Showing a Small Area of Carcinoma Occurring in a Predominantly Sarcomatous Tumor.*

centers of the larger tumor masses were necrotic, but peripherally the tumor was widely infiltrating the myometrium.

In still another case (Case 16), 1600 mg. hours of radium was applied within the uterus preoperatively. Twenty days later at laparotomy the tumor was too widespread (Fig. 1 and 2) for removal to be attempted, and material was not taken for histologic study at that time. The patient in Case 10 had an inoperable pelvic mass, and the only therapy was diagnostic curettage and radium. Unfortunately the exact dosage is not given, and the effect

FIGURE 8. *Carcinosarcoma (Case 13), Demonstrating Another Area from the Tumor Shown in Figure 7.*

of the radium on the size of the growth is not recorded. The patient survived eleven months.

In Case 15 x-ray therapy (2412 r) was given through each of two portals postoperatively because at operation small seedings of tumor were noted on the small bowel and in the liver. The patient died in three and a half months without showing improvement at any time. The patient in Case 13, described in greater detail below, received little or no benefit from x-ray therapy for recurrent tumor.

From the above cases, and the 2 patients with leiomyosarcomas previously mentioned as having received radiation therapy, one concludes that palliative roentgenotherapy is of little if any value unless it is to give the patient hope. The findings in Case 14 suggest that, as in carcinoma of the endometrium, preoperative radium destroys tumor projecting into the uterine cavity and thus prevents its dissemination in the operative field when the uterus is removed.

The following cases are of great interest in that the patients were treated with radium six and nine years prior to discovery of the sarcomas. Although the possibility seems remote, an etiologic role of the radium must be considered. These cases are presented in some detail because of the previous radium and because the courses are typical of those seen in patients with similar lesions.

CASE 9. G. B., a 48-year-old woman, in September, 1924, received 1000 mg. hours of radium for menopausal bleeding. Two 50-mg. capsules of radium in tandem were left in the body of the uterus for 10 hours. A curettage produced insufficient material for biopsy. The patient was well until 9 years thereafter, when she began to have episodes of right-lower-quadrant pain. She reported for treatment 7 months after the onset of symptoms, when the uterus extended two fingerbreadths above the symphysis pubis. A complete hysterectomy was done on December 31, 1934, and a mixed mesodermal tumor removed with the uterus. The uterus was lined by a ragged, necrotic, friable tumor measuring up to 2 cm. thick. Microscopically it was composed of undifferentiated, round cells with numerous areas of fairly well formed cartilage.

The patient was alive and well thirteen years postoperatively.

CASE 13. A. G., a 50-year-old woman, was given 1400 mg. hours of radium for menopausal bleeding in January, 1937. Curettage produced endometrium diagnosed as hyperplastic. She was well from that time until May, 1943, when she was admitted to the hospital after 2½ weeks of vaginal bleeding.

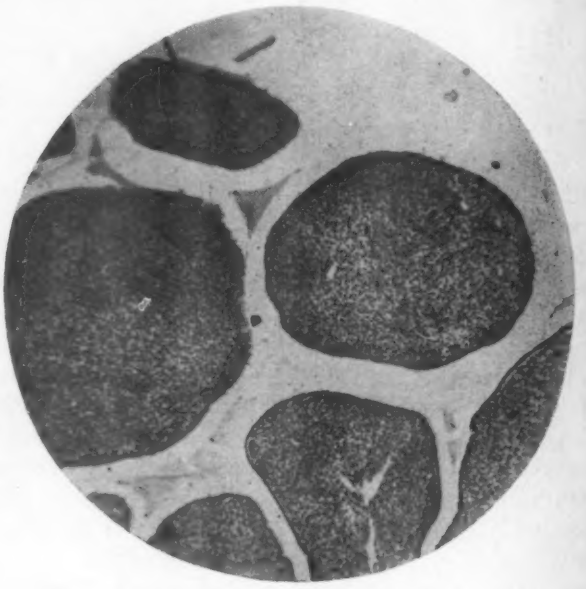

FIGURE 9. *Sarcoma Botroides (Case 18), Showing the Peripheral Grape-Like Projection.*

On May 21 a morcellation of what appeared to be a submucous fibroid presenting at the cervical os was done. Microscopically this turned out to be a sarcoma, which was called stromal cell. On June 4 a Wertheim hysterectomy was performed, and histologic examination revealed a few areas of epithelium (Fig. 7 and 8); the diagnosis was carcinosarcoma.

The patient had a local recurrence of tumor in 18 months and died of the carcinosarcoma 38 months after hysterectomy. X-ray therapy given on two occasions did not seem to influence the slow progression of the recurrent tumor.

The following case is also presented in some detail. Unfortunately, only four months have elapsed since operation and the ultimate outcome is uncertain, but the tumor is interesting enough histologically to warrant some discussion.

Case 18. J. S., a 5½-month-old infant, entered the hospital on January 15, 1947. She had been healthy from birth until 5 hours before admission, when she had a sudden onset of profuse vaginal bleeding. She appeared normal except for a firm, globular mass rising out of the pelvis to the umbilicus. Bleeding continued, and on the 2nd day a laparotomy was performed as a life-saving measure. The uterus was found enlarged and was opened in the midline, exposing a soft, grape-like mass of tissue measuring 5 by 5 by 0.8 cm. This was evacuated, leaving a smooth-lined endometrial cavity. A pathological diagnosis of sarcoma botroides was made, and further surgery was advised but refused by the parents in view of the poor prognosis regardless of treatment. The child was alive without evidence of recurrence 4 months postoperatively.*

Sarcoma botroides usually arises in the portio of the cervix and extends down into the vagina. In Case 18 the tumor filled the corpus uteri. Inasmuch as the exact origin of the tumor was not visualized at operation, but the entire endometrial cavity was smooth, it is assumed that the tumor arose from the cervix and for some reason protruded up instead of down.

Striated muscle fibers in a tumor of this type are considered pathognomonic of sarcoma botroides. They cannot be shown in this case but other characteristics are quite in accord with this diagnosis. Several areas within the tumor are of great interest histologically, since they help clarify the histogenesis of this tumor and possibly of others. There are large areas of a loose myxomatous tissue. The grape-like projections consist of closely packed cells with uniform, round, ovoid nuclei and little cytoplasm surrounded by cuboidal epithelium (Fig. 9). Most noteworthy are areas of tubules lined by columnar or pseudostratified epithelium (Fig. 10). These tubules closely resemble those of a fetal nephros, and structures simulating glomeruli can be picked out.

Wilms,[9] in 1899, advanced the theory that mixed sarcomas of the uterus originate in displaced myotome and scleratome elements carried down by the wolffian ducts. Glass and Goldsmith[10] concur in this opinion, and Case 18 seems to offer further support.

Summary

A brief account of the characteristics of various types of uterine sarcomas is given.

Eighteen cases treated at the Rhode Island Hospital since 1929 are recorded, and their classification is discussed.

A generally poor prognosis is recorded. The importance of few mitotic figures as evidence of a favorable outlook in leiomyosarcoma is supported.

There was a lack of evidence that leiomyosarcomas arise from pre-existing leiomyomas. In only 1 case were the two types of tumors found to coexist.

Eight patients received radiation therapy of some sort. X-ray treatment seems to be of little palliative value. One case appeared to be favorably influenced by preoperative radium applied to the uterus, as evidenced by necrosis in the subsequent pathological specimen.

Four cases reported in detail comprised a leiomyosarcoma with late metastasis to the humerus, a mixed mesodermal sarcoma and a carcinosarcoma occurring after radium treatment of menopausal bleeding, and a sarcoma botroides in an infant.

Figure 10. *Sarcoma Botroides (Case 18), Showing an Area Resembling Wilms's Tumor of the Kidney.*

I am indebted to Dr. George W. Waterman for his advice in the preparation of this paper, and to Dr. B. Earl Clarke for guidance in the study of the pathological material.

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*Information received after the preparation of this paper indicated that the patient developed a suprapubic mass ten months postoperatively and passed tumor tissue by vagina two months later.

THE PONDVILLE STATE CANCER HOSPITAL, 1927–1947

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SHORTLY after World War I, a movement was instigated in Massachusetts to provide care and treatment for patients with cancer. For many years various persons prominent in both public and private life became interested in the problem. The health officials believed that this was outside the realm of Public Health, but the public demands for some kind of a state-wide cancer-control program were so great that the Legislature in 1926 passed an act "to promote the prevention and cure of cancer and the extension of resources for its care and treatment." The bill originally called for the expenditure of $1,500,000 for the construction of a modern hospital to be located in or around Boston, but for some reason, no money was appropriated when the bill was passed. At that time there existed in the town of Norfolk, twenty-two miles south of Boston, on Route 1-A, a group of vacant buildings known as the Norfolk State Hospital, — formerly used by the Massachusetts Department of Mental Health for the rehabilitation of narcotic and alcoholic habitués, — which could be renovated and utilized for the proposed state cancer hospital. Therefore, the Legislature amended the original bill and appropriated $100,000 to renovate this group of buildings. Thus, Massachusetts became the first state in the country to appropriate funds for the construction and maintenance of a hospital to be used solely for the diagnosis and treatment of cancer.

The Massachusetts Department of Public Health, under mandate of the Legislature, opened the Pondville State Cancer Hospital on June 21, 1927. At first there was some question whether its 90 beds could be filled, but within a year the hospital was filled to capacity and had a large waiting list. Because of the demands, an addition for 25 beds was constructed, which only made a dent in the waiting list. The medical staff consisted of a medical superintendent and 4 residents, all graduates of surgical or rotating services of general hospitals. The nursing, in charge of a superintendent of nurses, was carried on by 19 graduate and 31 attendant nurses. A training school for attendant nurses was conducted with a course of one year. The visiting staff was made up of 17 men, all working on the cancer problem in other institutions in Boston or elsewhere, but none of them limiting their work to cancer.

The Pondville Hospital today has a capacity of 139 beds. These beds are in pavilions, each having numerous single rooms and several 2-bed and 4-bed wards. These pavilions have large airy porches, comfortable rooms and the necessary diet kitchens — in fact, all that helps to make a person who is ill and away from home and friends more comfortable. There are four operating rooms with equipment of the most modern type, two deep-x-ray-therapy machines, which are now considered essential in the treatment of cancer, a gram of that very expensive but very necessary element, radium, numerous radium needles encased in platinum and an electrosurgical unit. There are also chemical, bacteriologic and pathological laboratories, all essential to a modern hospital, and a medical library to keep the members of the staff informed of world trends in the progress toward the solution of cancer. Practically from its opening, this hospital has been approved by the American Medical Association and the American College of Surgeons, an indication that it meets in all particulars the exacting requirements of an up-to-date hospital.

The visiting staff, composed of 27 men representing all the medical and surgical specialties, receive salaries from the Commonwealth. Many of these men devote two and a half days a week to the work of the hospital, and others half a day; still others are called as the occasion arises. These men are all working on cancer in other institutions and are deeply interested in its problems. The resident staff consists of the medical superintendent, who lives on the grounds, and 10 resident physicians, all men who have graduated from surgical and rotating services of general hospitals.

One of the important services of this hospital is the general clinic for new and ambulatory patients and for follow-up work. Here consultations are held by groups of visiting surgeons, with a radiologist, an internist, a dentist and a laboratory technician present to make the necessary examinations. No matter how advanced the case or how obvious the condition, thorough examinations by x-ray study and other special procedures are made. Special clinics are held on other days by appointment for follow-up work. As in any good state cancer-control program, it is necessary to have a central focus of activity, so does the Pondville Hospital act as a nucleus for seventeen state-aided cancer clinics situated in seventeen cities and towns. Cases difficult to diagnose are referred from the clinics to Pondville.

The Social Service Department at Pondville is also an important factor in its work because in cancer, as in every disease, the early diagnosis and

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treatment depend not only upon the doctor's examinations and recommendations for treatment but also upon the patient's carrying out this advice. This, in turn, is dependent upon the patient's environmental conditions and economic resources, and it is here that the medical Social Service Department is of great value. The Social Service Department at the Pondville Hospital serves both the outpatients and the house patients. Thus, the Social Service Department, whenever possible, interviews the patient before he enters the hospital, assists him whenever and however possible while he is in the hospital and performs a valuable service in the follow-up work after he has been discharged. Uniform records are kept, and statistical studies are frequently made.

A volunteer social-service committee, comprising a group of women from neighboring towns, a local minister and a parish priest, provides many little luxuries for the comfort of both patients and employees. Recently, funds have been given to this committee by the Massachusetts Division, Incorporated, of the American Cancer Society to assist in the care and treatment of patients after they are discharged.

In 1928 the Legislature enacted a law regarding admissions and charges at Pondville. This act limits admission to residents of Massachusetts who have lived in the Commonwealth for at least twenty-four out of the last thirty-six months prior to the date of application and requires the written application of a registered physician or dentist. Persons who are able to pay their own bills pay $10.50 a week. If a person is unable to pay, the city or town in which he has a legal residence is assessed at the rate of $17.50 a week. Every patient, whenever possible, regardless of his financial status, is given a single room and as much individual attention as his condition requires. There is no classification of a ward or a private patient. The few wards of two and four beds are for patients able to be up and about. The Pondville personnel, from the lowest to the highest position, co-operate in giving the patient every service and in making him comfortable mentally and physically.

Daily visits are made by the priests and ministers from neighboring parishes, and current literature is distributed twice weekly for those requiring reading material. For those who enjoy the radio, bedside earphone attachments are available.

When a patient is discharged from the hospital, he is referred back to his family doctor or the clinic doctor who referred him to the institution. A letter is sent to this person giving the diagnosis, treatment and prognosis, with the advice that there be a continuous follow-up, both under his supervision and in the outpatient clinic of the Pondville Hospital. In this way harmony and co-operation are maintained between the hospital and the private physician.

TABLE 1. *Total Cases of Cancer from 1927 through 1946.*

DIAGNOSIS	MALE PATIENTS	FEMALE PATIENTS
Carcinoma:		
Buccal cavity and pharynx	1,893	166
Digestive system and peritoneum	1,566	661
Respiratory system	481	68
Female genital organs	—	2,017
Breast	18	1,685
Paget's disease	—	17
Male genital organs	528	—
Urinary organs	315	99
Skin	2,175	1,059
Other or unspecified sites:	244	173
Adrenal gland	3	1
Bronchus and neck	19	1
Neck, metastases (primary source unknown)	41	10
Eye and orbit	9	5
Hemorrhoid	—	1
Rathke's pouch	1	—
Thyroid	23	26
Urachus	1	—
Primary source unknown	75	49
Questionable	72	80
Other malignant tumors:		
Chordoma	1	—
Endothelioma:	7	7
Angioendothelioma	2	—
Endothelioma	1	3
Hemangioendothelioma	4	3
Lymphangioendothelioma	—	1
Epithelioma:		
Chorioepithelioma	—	2
Leukemia:	52	18
Leukosarcoma	1	—
Lymphatic leukemia	31	11
Myelogenous leukemia	16	6
Other leukemia	4	1
Lymphoma:	227	137
Giant follicle	9	1
Hodgkin's lymphoma	120	66
Lymphoma unclassified	45	29
Lymphocytoma	2	—
Lymphosarcoma	41	34
Lymphosarcoma (reticulum-cell type)	5	4
Mycosis fungoides	3	2
Thymoma	2	—
Polymorphous-cell sarcoma	—	1
Melanoma	75	70
Mixed tumor	5	3
Plasmacytoma	5	1
Sarcoma:	85	93
Adenofibrosarcoma	—	13
Adenomyosarcoma	—	3
Angiofibrosarcoma	1	—
Angiosarcoma	3	1
Fibrosarcoma	38	19
Fibrosarcoma, neurogenic	9	9
Leiomyosarcoma	6	25
Lipomyxosarcoma	2	—
Liposarcoma	1	3
Mixed-cell sarcoma	1	—
Myoblastoma	2	1
Myxofibrosarcoma	1	1
Myxosarcoma	2	5
Rhabdomyosarcoma	2	1
Sarcoma	12	12
Sarcoma, Kaposi type	4	—
Spindle-type sarcoma	—	—
Xanthosarcoma	1	—
Teratoma	8	—
Malignant tumor, type unknown	35	24
Questionable malignant tumor	19	10
Bone tumor:	76	44
Osteogenic	42	21
Chondroma series	8	2
Giant-cell tumors, malignant	1	—
Ewing sarcoma	11	5
Myeloma series	8	8
Malignant bone tumor, type unknown	2	1
Questionable malignant bone tumor	2	4
Chordoblastoma (embryonic remnant)	—	1
Tumors of dental origin (adamantinoma)	2	2
Tumor of nervous system:	11	12
Astrocytoma	—	2
Glioblastoma	2	—
Glioma	1	—
Medulloblastoma	1	1
Melanoma	—	1
Meningioma	—	1
Neuroblastoma	3	2
Neuroepithelioma	1	—
Retinoblastoma	1	1
Type unknown	—	3
Questionable	2	1

The purpose of the Pondville State Cancer Hospital is threefold: to provide adequate care for patients unable to be accommodated elsewhere; to stimulate more adequate diagnostic and therapeutic service for cancer in clinics; and to train physicians, surgeons and nurses in the diagnosis, treatment and general care of patients with malignant lesions. During the past twenty years, under the supervision of four successive commissioners of public health and three superintendents, the Pondville Hospital has hospitalized 21,277 patients, of whom 14,015 were new cases and 7,262 were readmissions. During the early days, upon admission the majority of patients were in the advanced stages of the disease, whereas in the last decade most of the patients were early cases and represented a fair cross-section of cancer as it has occurred in Massachusetts. Major operations were performed in 18,325 cases. The total deaths numbered 3,453, and in 57 per cent of the cases permission for autopsy was granted. In the outpatient clinics 101,943 patients were examined, of whom 19,153 were new cases and 82,790 patients were follow-up cases.

TABLE 2. *Subsequent Location of Physicians and Surgeons Trained at Pondville State Cancer Hospital.*

LOCATION	NO. OF MEN
Canada	2
China	1
Mexico	1
United States	120
California	1
Colorado	1
Connecticut	2
Delaware	1
Georgia	1
Illinois	3
Iowa	1
Kentucky	1
Louisiana	1
Maryland	1
Massachusetts	56
Mississippi	1
Missouri	1
Montana	1
New Hampshire	3
New Jersey	2
New York	13
Pennsylvania	7
Rhode Island	3
Texas	1
Vermont	2
Washington	2
Unknown	11

Table I includes all cases that were diagnosed as malignant, and since the members of the visiting and resident staffs have reported the results of the treatment given these patients in the current medical and surgical journals during this twenty-year period, no attempt is made to analyze these figures.

The Pondville Hospital, to date, has not only completed the first two of the original purposes for which it was established but also trained 124 physicians and surgeons in the specialized treatment of malignant tumors. Of these, 21 men received special training in pathology. Many of the men have settled in Massachusetts, and the others have settled in twenty-two states and three different countries. Many of these men have returned to their native states to practice and, so far as can be learned, are doing their share of the cancer work in their respective localities. This is particularly true of the 56 physicians who have settled in Massachusetts. Four surgeons have died, and the status of 11 other men is unknown.

Table 2 shows the location by country and state.

Fifteen years ago, the late Dr. George H. Bigelow, then commissioner of public health, and Dr. Herbert L. Lombard, director of the Division of Cancer and Other Chronic Diseases in their book entitled *Cancer and Other Chronic Diseases in Massachusetts* wrote "to give what would seem to be the most intelligent service in the field of recognition, cure, and alleviation, costs hundreds of thousands to millions of dollars." Truer words were never written, for the service rendered by Pondville during the last twenty years has cost the Commonwealth over $5,500,000, and

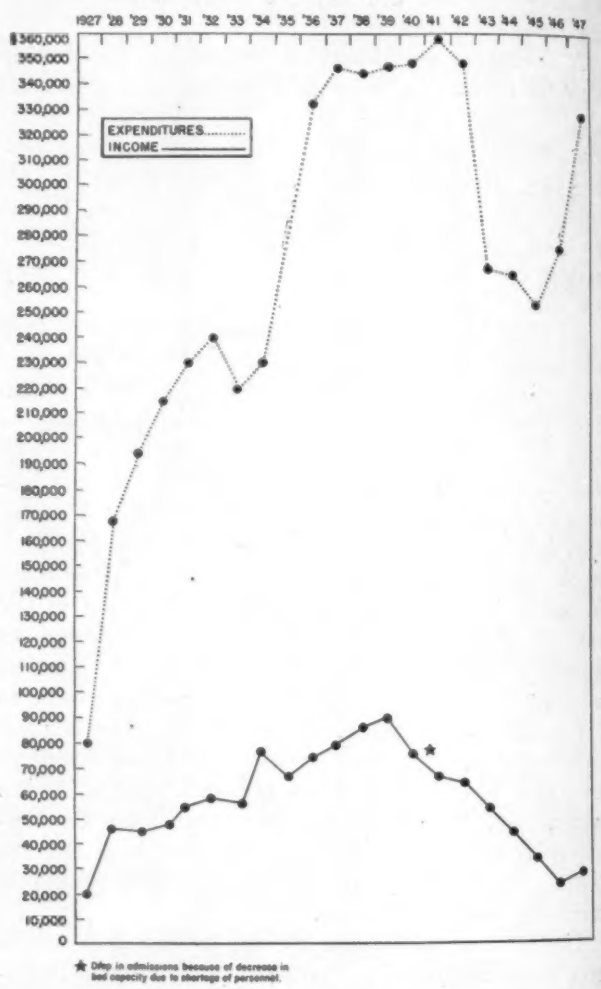

FIGURE 1. *Expenditures vs. Income Over Twenty-Year Period.*

this figure does not include the cost of additional building construction during this period. To be sure, more than $1,250,000 was collected from patients and the public-welfare boards in the various cities and towns as prescribed by the legislative acts of 1927, but the collections never balanced the expenditures (Fig. 1).

Figure 2 illustrates the fact that during the last six years the strictly indigent patient has been in the minority, for the greatest income has been collected from private sources — that is, from the

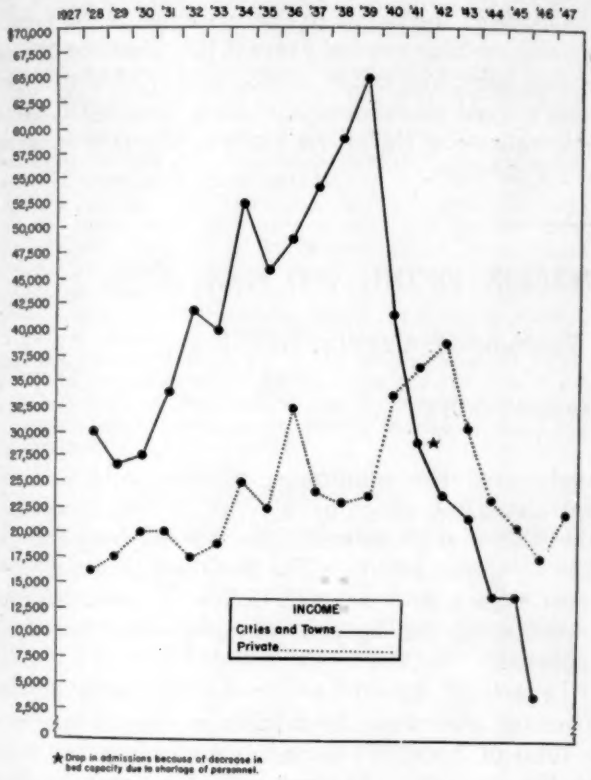

FIGURE 2. *Patient Income vs. Income from Cities and Towns over Twenty-Year Period.*

patient. However, the charge to the private patient represents only a fraction of the cost of treatment, and the greater part of the patients admitted are in fact medically indigent.

The ravages of World War II not only produced an increase of hospital expenditures but also caused a great upheaval in our hospital personnel. Like many other institutions, Pondville has been forced to decrease its active bed capacity to 40 patients because of the lack of graduate and attendant nurses. In spite of these factors, the turnover of patients in the hospital and in the outpatient clinics reached approximately prewar figures (Fig. 3). This was due to the careful selection and screening through the general clinic of the cases admitted to the hospital.

Table 3 explains the preceding charts and demonstrates the hospital activities on a yearly basis,

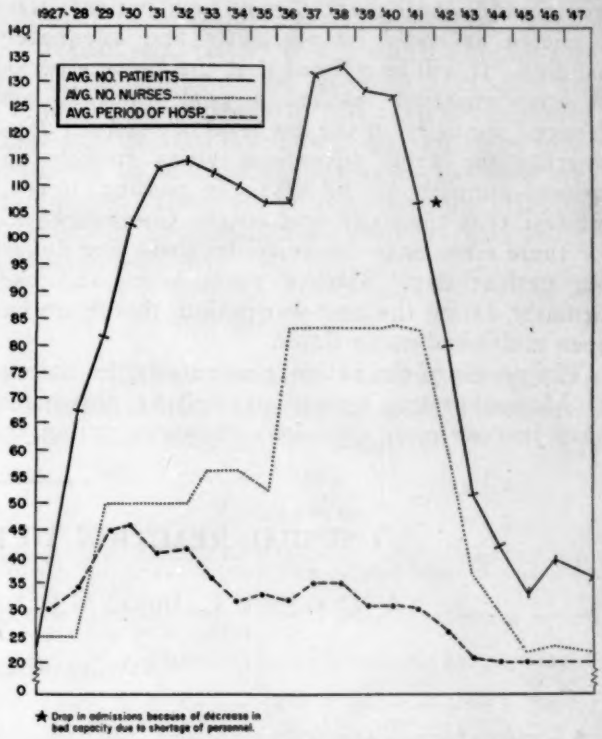

FIGURE 3. *Proportion of Active Beds vs. Available Nurses and Decrease in Average Period of Hospitalization over Twenty-Year Period.*

with special reference to the average number of house patients, the average period of hospitaliza-

TABLE 3. *Hospital Activities from 1927 to 1947.*

YEAR	AVERAGE NO. OF PATIENTS	AVERAGE PERIOD OF HOSPITALIZATION	AVERAGE NO. OF EMPLOYEES	TOTAL CLINIC VISITS
		days		
1927	23.2	30.30	50.0	133
1928	67.6	34.48	59.0	1,343
1929	82.18	46.83	75.0	1,502
1930	100.3	47.75	95.0	2,185
1931	113.5	43.99	110.0	2,805
1932	114.1	44.04	125.0	3,501
1933	102.0	37.3	130.0	4,429
1934	110.0	33.8	120.0	4,620
1935	107.0	34.0	144.0	4,638
1936	107.0	33.3	144.0	4,991
1937	131.0	35.4	191.0	5,332
1938	132.0	35.0	195.0	5,769
1939	128.0	31.3	196.0	6,908
1940	127.5	31.9	196.0	7,678
1941	106.0	30.3	196.0	7,654
1942	80.8	27.9	160.8	6,345
1943	51.6	22.4	112.0	6,084
1944	41.8	21.8	103.0	6,815
1945	34.1	20.5	89.51	6,205
1946	40.3	20.7	99.64	7,025
1947	40.75	19.01	110.8	8,085

tion, the average number of available employees and the outpatient clinic visits.

The peak of the patient and employee load was reached in 1938, and although the patient load fluctuated because of the type of cases admitted, the employee load remained constant until the year 1942. At this point the effects of World War II began to be felt, especially the lack of nursing personnel, and, consequently, only such patients were admitted as could be efficiently and adequately handled. It will be noticed that the average period of hospitalization reached a peak in 1930 and dropped annually to the low level of nineteen days, whereas the total outpatient visits steadily increased annually up to 8085. In passing, it is of interest that the daily cost to the Commonwealth for these services in the early days was five dollars per patient day. Twenty years later, and particularly during the post-war period, this figure has been multiplied many times.

The people of the nation, particularly the citizens of Massachusetts, laymen as well as physicians, have become more conscious of cancer during the last five years, and public opinion, having been aroused, has resulted in not only a greater need for beds for the cancer patient but also a demand for more intensive cancer investigation. In 1947 the Legislature, to meet the local needs, approved the expenditure of $600,000 for the construction of a power plant and a 100-bed nurses' home and recreation building. The Massachusetts Department of Public Health has recommended to the Legislature the expenditure of over $2,000,000 for additional buildings during the next five years to keep Pondville abreast of recent developments in the prevention and treatment of cancer.

Massachusetts citizens should be proud of the progress that the Pondville State Cancer Hospital has made in the battle to eliminate one of the greatest killers. For twenty years it has been the leader in this fight, and today stands as a tribute to those who worked so earnestly to make possible modern hospitalization for all its citizens who are in need of its services.

UNUSUAL REACTION TO PENICILLIN IN OIL AND WAX

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As new forms and combinations of penicillin have been developed, the reported incidence of hypersensitivity has also increased. Keefer[1] states that the incidence of hypersensitivity following the use of amorphous penicillin in aqueous solution has varied between 2 and 5 per cent. Although there is a belief that hypersensitive reactions are somewhat greater when penicillin in peanut oil and beeswax is used, conclusive evidence is not yet available.[2] Beeswax itself has been regarded as nonantigenic,[3] but some authorities think that certain persons may become sensitized to it.[1] Extensive studies have failed to show that pollen extracts are carried over in beeswax.[2] Some evidence has accumulated that the sensitization is to the penicillin itself and not to the oil and wax, for patients who receive penicillin in aqueous solution, after being sensitized by use of penicillin in oil and wax, have typical allergic reactions.

Romansky,[4] in a series of approximately 4000 cases treated with penicillin in oil and beeswax, reported allergic reactions in about 5 per cent. The reactions varied from slight urticaria to edema of the angioneurotic type. These reactions reached a maximum within four days of appearance. If the injection was given subcutaneously a local reaction occurred more frequently. Heat to the area aggravated the symptoms, whereas cold and the antihistaminic drugs gave relief. Thus, it appears that these reactions were truly allergic ones and not due to tissue injury. The Arthus phenomenon — local edema and necrosis following subcutaneous injection of the specific antigen — has not been reported.

Lederman[5] reported a case of severe local reaction after ten injections of penicillin in oil and beeswax, a total of 3,000,000 units having been given prior to the reaction. Another manufacturer's product did not give a reaction when the injections were resumed. Switzer[6] reported an acute local reaction one week after a single intramuscular injection of 300,000 units in a patient who had previously taken penicillin lozenges. In our practice 2 cases have exhibited urticaria and pruritus seven to nine days after a single injection of penicillin in oil and beeswax; no history of previous penicillin usage could be established. The third case is so unusual that it is reported in detail.

CASE REPORT

A 29-year-old married man was first seen on November 18 complaining of a furuncle of the left nostril, which had first been noticed on the preceding morning and had rapidly increased in size by the late afternoon. The only treatment had been hot compresses.

The past history was essentially irrelevant except for hypersensitivity to ragweed, which was controlled by preseasonal and co-seasonal desensitization treatment as well as antihistaminic drugs.

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Physical examination disclosed a furuncle the size of a small lima bean in the left nostril; the surrounding area was inflamed, firm and very tender. The nostril was almost completely occluded by the furuncle.

The temperature was 99.2°F.

At 9 a.m. the patient was given 300,000 units of penicillin in oil and beeswax (Romansky) intramuscularly in the anterior aspect of the midportion of the left thigh. Soon afterward some pain was present at the injection site. At 3 p.m. the area from there down to the left knee was tender to the touch, and active motion was painful. Three hours later the area was so sensitive that the weight of a blanket caused pain and motion was not possible. The temperature was 99.6°F., and headache and malaise were present. No signs of injury or tissue damage were visible, nor was there any change in the size or contour of the involved area. Treatment consisted of bed rest with ice packs and salicylates.

On November 19 the pain had diminished slightly, and some active motion was possible. Serous exudate was present at the left knee joint; the entire area otherwise appeared normal. Weight bearing was painful. Since the furuncle was still inflamed and firm the patient was given 100,000 units of crystalline sodium penicillin G in aqueous solution into the right buttock. No immediate hypersensitive reaction followed. Another similar injection was given on the following day, without reaction. In the next few days the symptoms gradually disappeared except that the left knee tired on walking. The furuncle was healed on November 23. Treatment for the left knee-joint exudate was ice packs, since heat aggravated the symptoms.

On the 9th day after the initial injection the entire area suddenly developed a pruritic urticaria, and the left knee-joint exudate reappeared. Pyribenzamine in 50-mg. doses controlled the pruritus. By November 28 the left thigh was 3 cm. larger than the right, and the skin on the anterior aspect had a thick, doughy texture. Very little pain was present, and normal activity was possible. On December 1 the left ankle was also swollen, being 2 cm. larger than the right. The left thigh was enlarged 2.5 cm., and the calf 1 cm. All edema was gone on December 5, and the only residuum was a nonindurated, red area at the site of the injection on the right buttock.

Discussion

Since the patient denied having previously received penicillin in any form, he was requestioned regarding his allergic history in an effort to establish an allergic basis for the early acute reaction. He stated that at least once each summer, during the period of ragweed allergy, the left knee joint became edematous and remained so for several days. Thus, one etiologic source in this case may have been the presence of ragweed pollen in the beeswax, although such pollen has not been found in beeswax in previous studies.[2] A second possible cause may have been an early serum-sickness type of reaction to the penicillin. Kendig and Toone[7] reported 3 cases in which a serum type of reaction developed five to seven days after oral administration of penicillin had been discontinued. These were delayed reactions characterized by fever, sensitivity to touch and swelling of the wrist and ankle joints. There are no reports in the literature on reactions to penicillin as early as that in the case described above.

Summary

A case of both acute early and delayed reactions to penicillin in beeswax and peanut oil is presented. Two possible etiologies are suggested.

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MEDICAL PROGRESS

PILONIDAL CYST AND SINUS

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THE ideal of all surgical treatment is to effect a cure, and in pilonidal cyst and sinus the basic aim is to prevent recurrence, lessen the period of disability and obtain a good mechanical result. The various methods presented in the literature by skillful surgeons attest to the fact that the search is not easy, although a number of men seem to have found the key to the problem.

This paper, therefore, presents a review of the literature, with a follow-up of constructive criticism, and the presentation of my technic, which is considered a rational approach to the problem and has resulted in 100 per cent cures.

Naturally, one would be less than human if he did not think his method superior, especially if excellent or relatively excellent results were usually obtained. One may disagree with the other man's procedure, or hold it in light regard. But it is best to remember that a certain method may work well in the hands of one surgeon and yet prove disastrous when another attempts it with seemingly the exact technic — the reward going to the former, who may have used certain imponderable niceties and nuances in the successful performance of his task.

Those who find a certain method newfangled or bizarre should keep in mind the following thought well expressed by Cutler and Zollinger[1]:

> Every change in the practice of surgery has aroused violent opposition. There was a battle between Lister and his opponents . . . the introduction of the x-ray elicited bitter criticism on the part of the conservative practitioners of that day. More recently the introduction of the electric scalpel and of the many forms of electricity for cutting and for coagulation has brought bitter opposition and slow acceptance . . . .

The term pilonidal cyst or sinus, from "pilus" (hair) and "nidus" (nest), comprises an abnormal opening in the midline skin superior to the anus in the gluteal cleft over the sacrococcygeal region. The defect is lined with epithelium, and may contain cellular debris, hair and sebaceous material. Sharpe[2] has written the following description:

> The tract is lined by poorly developed epithelium, and before the stage of infection, there may be some excretion of the products of skin metabolism through the orifice. If the orifice becomes blocked by accumulated debris or following an injury, the retained secretion may form a cyst or more commonly become infected and form an abscess. If the abscess ruptures without benefit of the surgeon, as is often the case, a fistulous opening is formed; if it closes, a secondary abscess may form later, and so the process may be repeated several times before the patient seeks surgical relief.

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According to Granet and Ferguson,[3] the term "pilonidal" is not necessarily correct, since most cysts do not contain hair. The authors state that the hair is extraneous and has its origin in the hair follicles of the skin of the natal fold adjacent to the sinus or dimple. Through the trauma of friction between the skin surfaces, some protruding hairs are broken off and retained in the sinus; through years of accumulation and by constant moulding from external pressure, they eventually become compressed and kneaded into hair nests.

TYPE

Gage's[4–6] classification is simple and clear: sacrococcygeal dimple and sacrococcygeal dimple and sinus; true pilonidal sinus confined to the subcutaneous tissue; true pilonidal cyst extending to the sacral canal; and true pilonidal cyst continuous with the subarachnoid space and canal of the spinal cord.

ETIOLOGY

Several interesting theories regarding etiology may help to explain the pathology and act as a guide toward rational treatment of this condition. Mallory[7] declares that the causation embraces the principle of captured ectodermal cells in the subcutaneous tissues and soft parts; the condition is due to captured ectodermal cells occurring at any stage during the development of the medullary canal or to faulty obliteration of the canal itself, or to a combination of both factors.

Weeder's[8] conclusion is that the included ectodermal cells may be limited to the soft parts, extending to and caught in the dorsal arches of the vertebras, or may be continuous with or captured in the medullary canal; or the latter may leave unobliterated remnants either with or without spina bifida occulta anywhere below the second sacral segment. They may extend to the skin through a sinus or remain as a cyst. It is interesting that Rogers and Dwight,[9] in a series of 400 cases, have found none to have communication with the neural canal, attesting to the rarity of this complication.

Fox,[10] in a detailed study, concludes that the pilonidal cyst is a congenital lesion due to a process of normal ectodermal invagination in the embryo,

which usually disappears but in these cases has persisted in adult life. It commonly contains fine, silky hair and mucoid or gelatinous material; it is almost always infected, and its walls consist of several layers of epithelial cells with glands and hair follicles. Derived from the budding or growth centers in the basal layer of the ectoderm that gives rise to hair follicles and glands, it consists of cells that form only hair and glandular appendages. For this reason, according to Fox, one never sees teratoma, neurogenic growths or heterologous tumors in pilonidal sinus.

Gage[4–6] is the chief proponent of the neurogenic theory: he believes that the condition is due to persistence of the neurenteric or neural canal. Normally, in the caudal end of the embryo, the portion of the neural canal that is formed by union of the neural folds and lies between the skin and coccygeal vertebras is obliterated by cohesion of its walls; failure to do so forms a cavity, which may be connected with the skin by one or more sinuses. The lining of the cystic cavity retains the faculty of producing the primitive skin appendages: the hair follicle or shaft, and a rudimentary type of nervous tissue if a connection with the spinal canal remains. Gage regards this as the true origin of pilonidal sinus and believes that the sacral dimple is the result of an anterior pull on the overlying skin by the caudal ligament as the coccyx grows downward and curves anteriorly.

Incidence and Distribution

Sharpe[2] states that 20 to 25 per cent of all infants examined at birth and about 4 per cent of a larger group of adults present either a distinct dimple or depression of the skin at the sacrococcygeal region. These always remain symptomless. Actual sinus orifices are seen less frequently, the exact incidence being unknown. The average age at which annoyance first occurs is nineteen years, with the incidence two or three times as great in males. McKirdie[11] states the incidence among Negroes as compared to that among whites to be 1:2150, or negligible, with no reports in the yellow, brown or red races.

Diagnosis

The sinus consists of small midline openings over the sacrococcygeal region, with an occasional tuft of hair protruding from the opening. When the sinus is infected, pus may exude from the openings. The area may be red, swollen and indurated, showing signs of a superimposed abscess.

Treatment

Roentgen-ray Therapy

Smith[12] uses roentgen-ray irradiation to prevent hair growth from interfering with healing, or to control infection. He presented 6 cases in which the final results were inconclusive.

Turell[13] reported a case in which 675 r was applied to the perineum and sacrococcygeal area over a period of two months; the sinus closed shortly before cessation of the treatment, and remained closed for five months; thereafter the patient disappeared, making it impossible to observe him further for ultimate results. In another case, 650 r was used over a six-week period, and the sinus has remained closed to date (two years).

Sher[14] obtained gratifying results in cases with a small sinus and small discharge and in cases with a short clinical history.

Sclerosing Solutions

Cutler and Zollinger,[1] observing the successful use of fixatives by the neurologists for gliomatous cysts, became interested in such a method for pilonidal cysts and sinuses. In the 3 cases presented, the roof of the sinus was incised, the edges being protected with zinc oxide, and the cavity filled with 1 to 5 cc. of modified Carnoy's solution (3 cc. of absolute alcohol, 3 cc. of chloroform, 1 cc. of glacial acetic acid and 1 gm. of ferric chloride). This was allowed to remain for five to ten minutes and then sponged out, and the destroyed tissue curetted away. This procedure was repeated every two weeks, at times daily; gauze was inserted after exposure to the solution.

Biegeleisen[15] presents 3 cases with a one-year cure. The sinuses are probed, and a modified Carnoy's solution is injected, a dull-tipped needle being used. Two weeks later the sinuses are curetted (2 per cent nupercaine being employed) with a fine curette or a needle having a long bevel, bent to form a slight hook; then fuming nitric acid is applied on an ordinary metal applicator deeply within the sinuses. Two weeks later this procedure is repeated. One month later it is difficult to enter the tracts, and still a month later the tracts are completely closed.

Mathesheimer[16] uses ethylaminobenzoate (twenty-five parts) and phenmethylol (seventy-five parts). The abscess or sinus is opened under skin infiltration. The tract is opened on a probe or grooved director at different stages, so as not to cause too large a wound. The wound is swabbed out, and plain gauze, saturated with the solution, is inserted; this procedure is repeated until healing has reached the surface.

Knowlton[17] uses 10 per cent sodium morrhuate, injecting 2 cc., and repeats the procedure in three or four days. Of 4 cases presented, 4 were completely cured.

Heyd[18] excises an ellipsis of skin carrying all the "dimples" and packing the cavity with modified Carnoy's solution. The gauze is left in for forty-eight hours, and the procedure is repeated in a few days, with plain gauze left in between. Twenty-

five cases were presented, all successful. Heyd claims that this method makes the walls of the wound rigid and firm, and that the cavity heals readily and rapidly.

Shafiroff and Doubilet[19] used a mixture of penicillin and sodium morrhuate (5 cc. of 5 per cent sodium morrhuate to 100,000 units of dry penicillin); 1 cc. was injected directly into the cyst or sinus tract the first time, and as sclerosing progressed, small amounts were injected daily and then every other day. Twenty-seven cases were presented, with a minimum of four to a maximum of forty-six injections. After two or three injections the drainage from the orifices subsided rapidly. A follow-up study over a three-month period showed recurrences in 3 cases.

Cautery Excision

Rogers is a leading exponent of the use of the cautery knife. In a series of 181 ambulatory cases this technic was employed by Rogers and Hall.[20] The method, in brief, consisted in repeated excision with cautery of the diseased tissue. The sinus was first divided longitudinally down to the sacrococcygeal fascia, and then removed in halves by slight undercutting of the skin edges. Postoperatively, further fractional removals were effected for portions overlooked originally. The loss of time from work was less than two weeks. At the time of publication, Rogers and Hall believed that there was room for improvement. In an article written in 1938 Rogers and Dwight,[9] concluded that it was not necessary to remove or expose the sacral fascia. At that time, in a large series of cases of undisclosed number, 90 per cent were cured in less than fourteen weeks, 80 per cent in less than twelve weeks, and 64 per cent in less than ten weeks, with a minimum of five weeks. In a 1940 publication, Rogers[21] recommended conservative cautery excision under a local anesthetic in the outpatient department. The sinus tract and hair nest were dissected out through the midline skin incision with the small cautery blade; the resultant narrow wound was packed with gauze. The shortest healing time was four weeks, with an average of nine weeks. One hundred and fifty operations were done between 1935 and 1937, 14 in the hospital and 136 in the outpatient department, and 97 per cent were cured by conservative excision, remaining cured for one to four years. On this basis, Rogers is against large block excision.

Hipsley[22] excises the sinus by cautery and then makes an incision 7.6 cm. lateral to the wound above the ischial tuberosity in the line of the fibers of the gluteus maximus muscle; a flap of muscle sufficiently thick to fill the cavity and to reach the opposite wall through the tunnel without tension is freed, the wound being closed loosely

Marsupialization

Dorland[23] defines marsupialization as an operation for hydatid or other cyst in which the tumor is opened, its contents emptied, and its edges stretched to the edges of the external incision. The interior of the sac so formed suppurates and closes by granulation. Buie,[24] one of the chief exponents of this method, argues that the deeper half of the lining of the cyst cavity, since it was originally intended to form skin, can be used to advantage in the surgical management of the problem. The operation makes use of the deep half of these membranes, whether part of the unaltered cyst cavity, abscess cavity or fistulous channel. Buie further adds: "If there has been no destruction by inflammation or erosive changes within the walls of the cyst or sinuses, this membrane will possess practically the same histologic structure as that of true skin and is therefore peculiarly fitted for the purposes of the operation." He leaves intact the inner wall of the cyst and its branching tracts; the skin edges are sutured to the margins of the remnant of membrane that originally enclosed the cyst, the cyst having been first unroofed and the redundant skin edges and outer half of the cyst wall having been trimmed away. The floor of the cyst then becomes the external surface.

Brockbank and Floyd[25] recommend radiant heat for fifteen minutes twice daily to keep the wound dry and to encourage epithelialization, having returned 90 per cent of 168 patients to military duty in twenty-one to twenty-eight days with complete healing.

Peterson and Ames,[26] Van Dyke,[27] Henning[28] and Nesselrod[29] are all enthusiastic adherents of this method. Nesselrod gives the following caution: "The most annoying problem, and one which is a source of embarrassment both clinically and statistically, is the occasional failure of mid-line healing." For this, he recommends bed rest, ultraviolet-ray therapy and surgical revision of the skin edges.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 34231

PRESENTATION OF CASE

A sixty-seven-year-old man entered the hospital complaining of weakness, anorexia and vague abdominal distress.

The patient had always been in good health until six months before entry, when he began to notice intermittent, vague, abdominal distress not associated with meals. These symptoms persisted, and three months before entry he noted a vague feeling of abdominal distention without the passage of gas. There were no cramps, pain, diarrhea or bloody stools, but he noticed increasing constipation and darker stools. There was no jaundice or dark urine. Gradually he became increasingly more anorexic and lost 15 pounds in weight in three months. He began to have dyspnea on exertion but denied orthopnea, anginal pain, ankle edema and paroxysmal nocturnal dyspnea. An electrocardiogram was normal. For two months prior to admission he noted slight cough, with the expectoration of brownish sputum flecked with blood. In the past a deviated nasal septum had given rise to epistaxis, but he had had no recent difficulty with his nose to account for the hemoptysis. For the month before entry he felt so weak that he was unable to leave his home. Two gastrointestinal series, a cholecystogram and a chest film taken elsewhere were reported as being normal.

Twelve years before entry a prostatectomy for benign hypertrophy was performed, but the patient had no urinary symptoms except occasional nocturia.

Physical examination on admission revealed a somewhat pale man showing evidence of moderate weight loss. There was no jaundice or peripheral lymphadenopathy. The heart was enlarged to the left, the border of cardiac dullness being 2 cm. outside the midclavicular line. The aortic second sound was greater than the pulmonic second. There was a Grade II harsh systolic murmur at the apex. There were signs of fluid at the right base with dullness, diminished tactile fremitus, diminished breath sounds and diminished whispered voice. Examination of the abdomen was entirely negative, as was examination of the extremities.

The temperature was 97.6°F., the pulse regular at a rate of 120, and the respirations were 20. The blood pressure was 170 systolic, 100 diastolic.

Examination of the blood disclosed a hemoglobin of 14.6 gm. and a white-cell count of 11,500, with 88 per cent neutrophils. A blood smear showed some variation in size of the red cells, with stippled cells and bizarre-shaped forms. Urine examination showed a rare red cell, 4 white cells and 2 epithelial cells per high-power field. One stool was brown and gave a negative guaiac reaction, but three subsequent ones gave strongly positive guaiac reactions. No ova or parasites were seen in the stools. A test for neutral and total fat in the stools was +. Two bromsulfalein tests gave 38 per cent and 28 per cent retention of dye in the serum. Urobilinogen in the urine was present in a dilution of 1:500. A van den Bergh test was negative, and the prothrombin time was 22 seconds (normal, 17 seconds); the blood vitamin A was 0.8 mg., the carotenoids 0.7 units, the serum amylase 40 units, the cholesterol 203 mg., and the serum protein 8.25 gm. per 100 cc., with an albumin-globulin ratio of 1:1. The nonprotein nitrogen was 28 mg., and the blood sugar 112 mg. per 100 cc., and the cephalin-flocculation test was negative at twenty-four and forty-eight hours.

A barium enema, which was not entirely satisfactory because of poor preparation, showed no definite organic disease except two diverticula in the proximal transverse colon.

In the hospital the patient was observed to be very dyspneic and after several days began to develop sacral edema and moist rales at the left base. He was given digitalis, and an electrocardiogram taken several days after the digitalis was started showed sinus tachycardia, with evidence of digitalis effect on the ST segments and T waves, but no definite diagnosis of cardiac disease could be made. His appetite was very poor, and a Levine tube was introduced into the stomach to force feedings. All physicians who saw the patient believed that he was quite ill, and one observer noted, "He is sicker than he looks." All efforts at therapy were to no avail; the patient began to vomit blood, became more dyspneic, gradually became unresponsive and expired quietly on the twelfth hospital day. The temperature had remained at normal levels throughout the hospital course.

Differential Diagnosis

Dr. Earle M. Chapman: In brief, the Pathology Department has invited me to make a diagnosis — I would even say that they have defied me to make a diagnosis. This was a sixty-seven-year-old man, who complained of being ill for six months, with weakness and anorexia and, I should say, asitia (a loathing of food) and vague abdominal distress. A careful investigation, including physical, roentgenologic and laboratory examinations, failed to provide an adequate diagnosis or even to give a clue. There is one small clue — a series of what I call dissociated signs of some impairment of liver function. Perhaps it would be well to discuss the one positive set of signs that we have — namely, the changes in liver function. In the first place, we find that the Graham test was reported elsewhere as being normal, and yet in this hospital a bromsulfalein test showed 38 per cent retention of dye in the serum, which is abnormal. There was urobilinogen in the urine and some bizarre-shaped red cells and stippled cells, but there seems to be very little evidence of blood destruction. The van den Bergh test was negative, and the prothrombin time very slightly elevated, almost normal; there was a depletion of the carotenoids, and some depression of the serum protein. What do these signs indicate? I cannot accept the diagnosis of cirrhosis. But it seems that, from these tests, cirrhosis of the liver certainly had been entertained as a likely diagnosis. This was reasonable because the description of the final illness clinically reads like cholemia. It sounds like liver failure — what I believe Europeans used to call cholemia.

There are two or three red herrings that cross the trail. One is the coughing of blood, and the other, the positive guaiac reactions in three stools, indicating a lesion in the gastrointestinal tract. The x-ray films did not reveal such a lesion, and yet this would again fit with the clinical impression of cirrhosis. Esophageal varices that were leaking were considered, and this could also account for the final episode of the vomiting of blood. An alternative explanation for the stools is that the patient was swallowing sputum from the right bronchus that contained blood, and this would better explain the intermittent positive guaiac reactions in the stools.

What are some of the things that we have to consider? Let us go back to the past history. A prostatectomy was performed twelve years before admission. Did the patient have a malignant tumor that had arisen in the prostate and involved the urinary tract? I do not see any evidence on which to base such a diagnosis and so I discard it. Was it a primary malignant lesion arising in the right main bronchus? We have the signs of fluid at the right base, dullness, diminished tactile fremitus, and diminished whispered voice — in other words, not only fluid but occlusion of the bronchus leading into the right lower lobe. Apparently no x-ray films of the chest are available.

Dr. Stanley M. Wyman: No; just of the colon.

Dr. Chapman: Considering the definite cardiac changes, peripheral edema and dyspnea, did the patient have some form of underlying heart disease? We are told that the electrocardiogram was normal. No one seems to have made the diagnosis of heart disease, but I seriously entertain the possibility that this man at sixty-seven had calcific aortic valves. Calcific aortic stenosis is often overlooked in the older age group, and the signs are quite variable. He had a harsh systolic murmur and an elevated blood pressure, and finally died, with some of the symptoms of congestive failure. He did not respond to treatment. In trying to put the facts together, having entertained the other possibilities, we must consider some form of heart disease.

We must also consider carcinoma of the pancreas — in the body, of course, because the stools were colored, and there is no indication that a tumor mass was felt. But we must consider a small carcinoma of the pancreas with metastases to the liver and perhaps the lung on the right side. Carcinoma of the body of the pancreas is one of the most difficult diagnoses to make on clinical grounds, and in the case under discussion, there was no pain of pancreatic distribution or other signs to indicate such a lesion.

We must think of some rare disease involving a limited area of the liver, causing dissociated signs. The only disease that I can think of is primary tumor of the liver — a hepatoma. If the patient had a primary carcinoma of the liver, we must in all likelihood suspect an underlying minor degree of cirrhosis. I believe Dr. Mallory has taught us that in primary liver tumor there is always the coexistence of some degree of cirrhosis.

Dr. Tracy B. Mallory: There was in all but one case in the records of this hospital.

Dr. Chapman: I think that Dr. Mallory will have to tell us what was wrong. I cannot say anything except a malignant tumor involving the liver because of the clues that I have mentioned. If I have to make a diagnosis, I shall say hepatoma — whether it spread into the right chest and perhaps produced fluid or whether there was a metastasis in the region of the bronchus with erosion, it is impossible for me to say. The patient may have had an underlying calcific aortic stenosis.

Dr. Wyman: The examination of the colon was unsatisfactory as the record notes because of the extremely large amount of fecal material. One can outline the lower border of the liver, but the upper margin is lost. One cannot say that the liver is grossly enlarged from these films. The spleen does not appear to deform the splenic flexure; it lies in normal position. The bones show no definite evidence of destruction that I can see. I see no definite abnormal soft-tissue masses. It is impossible to exclude a lesion of the colon, however.

Dr. Chapman: Was a gastrointestinal series done by you, with study of the second portion of the duodenum, the possibility of pancreatic involvement with tumor and ulceration being borne in mind?

Dr. Wyman: No; it was done elsewhere.

Dr. Briant L. Decker: How about a myeloma with involvement of the liver? The serum protein was in the upper limits of normal, and the albumin-globulin ratio was 1:1.

Dr. Chapman: I have myeloma written on the border of my copy of the abstract. I thought it unlikely and that the change of protein was consistent with liver disease, and so I excluded myeloma. One has to think of it with the reversal of the albumin-globulin ratio, but as I say, I prefer to let the liver take care of that.

Dr. Alfred Kranes: I cannot think of a case of myeloma without anemia. I may be wrong about that. Is that correct?

Dr. Mallory: Yes.

Mr. George A. McLemore, Jr.: Could the high urobilinogen have been caused by the gastrointestinal bleeding?

Dr. Chapman: I do not know, but I doubt it. That is all I can say.

Clinical Diagnoses

Liver failure, probably from portal cirrhosis.
Arteriosclerotic and hypertensive heart disease, with congestive failure.

Dr. Chapman's Diagnoses

Malignant tumor of liver (hepatoma ?).
Metastases to lung.
Calcific aortic stenosis.

Anatomical Diagnoses

Adenocarcinoma of pancreas, with metastases to liver, lungs, left adrenal gland and serous surfaces.
Pulmonary emphysema.
Hypertrophy of heart, hypertensive type.
Thrombosis of segment of inferior vena cava and both common iliac arteries.

Pathological Discussion

Dr. Mallory: Post-mortem examination showed extensive neoplasia. The pleural and abdominal cavities were both studded with minute tumor nodules; the lungs showed extensive involvement of the pleura, extending a very short way into the parenchyma of the lung, but nothing that suggested a primary tumor. The liver was small, weighing only 1500 gm., but showed a large number of very small tumor nodules. In the body and tail of the pancreas was a large mass of tumor — the only large mass that we found. The histology was entirely compatible with a primary pancreatic tumor. I do not believe there is much question about that. I still think that we have a very inadequate explanation of the peculiar laboratory findings as related to liver failure. It takes a great deal of cancer of the liver to produce any liver failure. Usually, when metastasis to the liver is extensive enough to cause liver failure, we find the organ grossly enlarged, weighing 3000 or 4000 gm. This liver was on the small side of normal. On the other hand, the total amount of tumor in proportion to the size of the persisting liver tissue was high. I suppose we must assume that the liver metastases were responsible for the liver failure. There was nothing to suggest any primary abnormality of the organ. The cells were in good shape, and there was no bile stasis, no fatty vacuolization or anything else that one could consider primary liver disease.

We did not find any evidence of calcific aortic stenosis though the heart was generally hypertrophied as in hypertension. There was a saddle thrombus of the vena cava extending into both iliac veins, but no pulmonary emboli of significant size.

Dr. Kranes: The laboratory findings in themselves are inconsistent. I did not believe that it was possible to have a normal cholecystogram with a bromsulfalein retention of 30 per cent. One or the other is wrong.

Dr. Mallory: I think that there was a fair time interval between the two examinations.

Dr. Chapman: Yes; the Graham test was done before he came in and the other was just before he died.

Dr. John Stanbury: How much pleural fluid was there?

Dr. Mallory: A few hundred cubic centimeters.

DR. CHAPMAN: Was there no gross area of erosion in the gastrointestinal tract?

DR. MALLORY: No; there was one small bronchus invaded by tumor, which might have accounted for the hemoptysis, but not for extensive bleeding.

CASE 34232

PRESENTATION OF CASE

A fifteen-year-old boy entered the hospital because of a mass in the left calf.

Five years prior to admission without antecedent trauma he noted the gradual onset of pain on the medial side of the left calf. It occurred only during exercise, was not severe and did not limit his activities in any way. Approximately three years before admission he noted a lump in this area, which was tender to touch. No particular motion caused pain, and there were no paresthesias. He noted that the heel of the right shoe wore out more quickly than the left. There was no weight loss or constitutional symptoms.

Physical examination showed a well developed and well nourished boy, the positive findings being limited to the left leg. There was full range of motion in the hip, knee and ankle except for dorsiflexion of the left foot, which was limited, the foot being held in about 15° of equinus. With the knee flexed the foot could be dorsiflexed an additional 10°, but it could not be brought into the normal amount of dorsiflexion; motion in plantar flexion was normal. There was no muscle weakness or sensory change. The knee jerks and ankle jerks were active and equal. The circumference of the calf was 1.2 cm. less on the left than on the right. On inspection there was slight prominence in the region of the belly of the medial head of the gastrocnemius, and on palpation a mass could be felt in this same region, approximately 2.5 cm. long and 1.5 cm. wide. The mass appeared to be within or immediately beneath the gastrocnemius muscle. It was of firm consistence, nontender and not adherent to subcutaneous tissues or skin. No bruit could be heard. No lymph nodes were felt in the popliteal or inguinal regions.

The urine was normal.

X-ray examination of the leg was essentially negative.

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN A. REIDY: With the information at hand we can at least decide why this boy wore his right heel out more than the left in that the Achilles tendon on the left was necessarily contracted, giving the equinus position as described in the x-ray report. This kept the left heel from striking the ground or at least from striking the ground as firmly as the right. I venture to say that he probably had more wear on the toe and sole of the left shoe than on the right, although that fact is not mentioned. We can assume that the equinus deformity was probably due to contracture of the Achilles tendon, particularly in view of the fact that there were no changes in the foot or ankle. Motion was fairly complete except for this lack of motion in dorsiflexion, and since x-ray films of the foot are not mentioned I take it that they were normal.

We can now direct our attention, I believe, to the firm, nontender mass that lay beneath the medial head of the gastrocnemius muscle. It probably would be well to review the x-ray films.

DR. STANLEY M. WYMAN: I am sorry, but we do not have the films.

DR. REIDY: It would be worth while to know if there was a soft-tissue shadow — it might help in better localization of the lesion. If it was down the shaft distally beneath the gastrocnemius, it would present a different picture than it would if located beneath the gastrocnemius in the proximal portion in relation to the popliteal space, where there are numerous cysts, ganglions and so forth that arise from the posterior aspect of the knee joint. If the shadow were in relation to the knee joint, it might help us somewhat. The x-ray films apparently do exclude evidence of bony disease or tumor. We can therefore confine our thoughts more or less to the soft tissues.

This lesion was a chronic one, which had been asymptomatic for five years and palpable for three years. The size is mentioned as apparently remaining the same, although it may have increased. If it did, it certainly did not increase very much — 2.5 by 1.5 cm. is not a large lesion and can easily be obscured. The chronicity, the lack of pain and the good general health of the patient, I believe, are helpful in ruling out the possibility of any malignant tumor. Certainly, fibrosarcoma, which is one of the more common tumors in this region, would have manifested itself much more clearly and more definitely than this tumor.

Rhabdomyoma, a skeletal-muscle tumor, which I have seen in the medial head of the gastrocnemius, is a rare lesion and I doubt that it was present in this case. Certainly, it would have been more evident.

There have been reports of synoviomas removed from the region of the knee several years after the original tumor was noted. These are slowly growing tumors and could account for the symptoms in this case.

A low-grade infectious process such as tuberculosis, I think, is a remote possibility, but there is nothing to substantiate that diagnosis.

An organized hematoma or subsiding myositis ossificans could possibly have caused this difficulty. It is unlikely, however, particularly in view of the lack of trauma or changes on the x-ray films.

An angioma or aneurysm can readily occur in this region in relation to the popliteal vessels, but here again I think the tumor would have been soft, at least softer than that described, and would perhaps have caused a bruit, which is said not to have been present. Lipoma, similarly, is a soft tumor and probably would not have resulted in the irritation and pressure that caused this contracture of the Achilles tendon.

Chondroma is a possibility in that it can occur in the region of the knee joint, extend down beneath the gastrocnemius, and not cause a shadow by x-ray study, although there may be evidence of some soft-tissue distortion. That is unlikely, however, because it is such a rare lesion, as is a fibroma occurring alone. The fibroma is more likely to arise in the hand or foot than in this region.

There are other possibilities — either a Baker's cyst or a neurofibroma. Baker's cyst is an extension of the bursa that lies in relation to the semitendinous muscle and beneath the medial head of the gastrocnemius muscle and can dissect down beneath the muscle for a considerable distance. With the knee in extension this forms a dense, frequently nontender, tumor and may cause minimal or no symptoms. It is a possibility. Yet I think that a solitary, slowly growing, nontender neurofibroma, which is one of the more common tumors that occur in this region, can produce this picture, and on the basis of frequency I shall make that diagnosis.

Dr. Joseph S. Barr: The mass was in the most prominent portion of the medial head of the gastrocnemius muscle, about 15 cm. distal to the knee joint. We did not believe that it was a ganglion or that it was related to the knee joint. The sole x-ray film taken was for the purpose of determining whether or not there was a soft-tissue mass, but we could not see any. The mass was definitely palpable in or beneath the gastrocnemius muscle. Some years ago I had a patient, a boy about the same age, who had a tumor in this location that proved to be a hemangioma. The tumor in the case under discussion had no bruit and was hard and firm. I was a little indefinite in my preoperative diagnosis, finally settling for a tumor of the gastrocnemius muscle.

Clinical Diagnosis

Tumor of gastrocnemius muscle, ? hemangioma.

Dr. Reidy's Diagnosis

Neurofibroma.

Anatomical Diagnosis

Cavernous hemangioma of head of gastrocnemius muscle.

Pathological Discussion

Dr. Barr: The tumor, which infiltrated the whole medial head of the gastrocnemius, was spindle shaped and quite firm. The tumor infiltrated the muscle and had no capsule; it involved at least half the medial head of the muscle. The whole of the medial head of the gastrocnemius muscle was excised.

Dr. Reidy: Did you make a diagnosis on the gross specimen?

Dr. Barr: I could not have, although we called Dr. Castleman to see it and he called it a hemangioma grossly. I believe that was the final diagnosis. It was a solid tumor with large blood vessels infiltrating into it. It was so solid that I questioned the diagnosis.

Dr. Tracy B. Mallory: Microscopical sections showed a characteristic cavernous hemangioma. The tumor was surrounded by a considerable degree of inflammatory reaction. The hardness may have been due to inflammation rather than tumor.

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ACUTE LEUKEMIA: PRESENT AND FUTURE

In an article published elsewhere in this issue of the *Journal* it is pointed out that the parenteral administration of certain folic acid antagonists is not infrequently followed by clinical and hematologic remissions in children with acute leukemia. The authors very properly stress the fact that these remissions, though somewhat prolonged, must not be regarded as cures.

Many years ago the hope was implied that acute leukemia was a potentially curable disease.[1] This hope and this belief stemmed from the undoubted fact that a moribund patient with unquestionable, acute leukemia went into a prolonged and complete remission after the parenteral administration of what was assumed (probably erroneously) to be adenylic acid. The remission was, however, almost certainly spontaneous, and the original disease reappeared in an explosive manner some five months later. In a very short time the patient was dead.

Subsequently a series of cases with acute leukemia of one sort or another with dramatic remissions of considerable duration was reported in the *American Journal of Cancer*.[2] Individual reports of similar remissions have appeared in standard medical journals from time to time, and still other patients have been seen but not reported. In one case a remission lasted approximately thirteen months. Some of these remissions appear to be truly spontaneous; occasionally they follow the subsidence of an acute infection. Of the 5 cases reported by Farber et al. initial remissions of this type occurred in 2.

Therefore, the possibility of a spontaneous remission must be entertained whenever a patient with acute leukemia becomes apparently well from both a clinical and a hematologic point of view. Yet so far as is known practically all such patients have subsequently died in relapse. Of the extremely rare case in which the patient did not die it may be said that the original diagnosis was incorrect.

Precisely what the bone marrow showed in these cases during the remission is not known, but as all lymphadenopathy and splenomegaly disappeared and the peripheral blood picture became entirely normal in all respects it may be assumed that the bone marrow in like manner and to like degree became normal.

This, then, is the first point: it is well known that spontaneous remissions — complete and of considerable duration — may occur in acute leukemia. It is not argued that the remissions referred to in the article under consideration were, in fact, spontaneous. It is simply pointed out that such remissions have occurred.

The second point is this: when the parenteral administration of a substance, of whatever nature, is followed by remission in leukemia one should be extremely cautious before one even implies that a true cure might result. The physician experienced in the care of leukemic patients and versed in the pitfalls of experimental work will scarcely be led astray. The practicing physician who does not specialize may grasp at this straw and overplay his hand. Believing that the earlier a case is treated the greater is the chance of success, he may treat patients whose

blood picture is suggestive of but not diagnostic of acute leukemia. And the layman — he who reads the daily press, which is no proper medium for the announcement of therapeutic measures still in their experimental stage — will not only grasp at the straw but also perhaps twist and turn even the most cautious expressions to his own supposed advantage. He may fail to distinguish between "arrest" and cure, and he may brush aside as improbable or inconsequential the third point: with the introduction of new therapeutic measures, even those of proved value, the beneficial effects stand prominently in the foreground and the deleterious and occasionally fatal side effects are either unrecognized or minimized. Such is the story of aminopyrine, arsenic for the treatment of leukemia, and sulfonamides and latterly folic acid.

There is some evidence, as yet unpublished, that the administration of aminopterin may be followed by refractory pancytopenia, and a similar sequence of events might follow the use of newer compounds as yet unsynthesized. It may be argued that such side effects as may occur in the treatment of acute leukemia with folic acid antagonists may be regarded as unimportant in view of the practical certainty of death in that disease. Yet whether these side effects may in themselves be fatal or permanent is not yet known, and, more important, the positive diagnosis of acute leukemia is not always easy. Physicians of international fame have been known to be wrong in its diagnosis. This being the case, it is possible that those who read the *Journal* might similarly be in error.

Clinical investigation must not be limited, and the early publication of experimental work should not be delayed once competent and unbiased observers believe the work to be well founded. It is proper and necessary, however, to be cautious to a fault.

The experimental data briefly and guardedly presented in this issue shed new light on the problem of leukemia, and we may, now, with some justice hope that aminopterin or some substance related to it, as yet unsynthesized, will afford a substantial basis for real hope in this now hopeless disease.

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MENTAL HEALTH AND WORLD CITIZENSHIP

The International Congress for Mental Health, to be held this summer in London, will have the formation of a world federation for mental health as one of its most important objects. The subject for discussion at this world congress — Mental Health and World Citizenship — will be broken down into five main headings: problems of world citizenship and good group relations; the individual and society; family problems and psychologic disturbances; organization, training and propaganda in planning for mental health; and mental health in industry and industrial relations.

To obviate the possibility of each group discussing its topic and arriving at its conclusions quite independently of the others — as might be the case if "specialists" only took part in the discussions — mixed committees have been set up for the consideration of each subject. These committees will be composed of a variety of elements — psychologists, psychiatrists, sociologists, educators and anthropologists. Co-operating in plans for the Congress have been Dr. Brock Chisholm, executive secretary of the interim commission of the World Health Organization, and Dr. Julian Huxley, director general of UNESCO — the United Nations Educational, Scientific and Cultural Organization.

Dr. Chisholm, in a short paper published in *Survey Graphic* in October, 1947, outlined the world's need for a supreme effort in the direction of more universal mental health. Man, in a physical sense, is becoming the master of his environment. The material obstacles to survival he has been slowly conquering, one by one — the hazards of climate, of inadequacy in food supply, of disease. The really great obstacle that remains is man himself with his highly developed intellect that he cannot use effectively because of "his neurotic fears, his prejudices, his fanaticisms, his unreasoning hates, and equally unreasoning devotions."

This, paradoxically, is today the great threat to man's survival in a world that he has otherwise tempered to his needs — the presence of other men of other races, of other creeds, of other ideologies in

that world, and their inability to live in harmony together.

So great a control has man today over various environmental situations that a few men of ill will may obtain the power of affecting the destinies of millions. A single pyromaniac may destroy a forest that has been a century in growing; a small nation may have the means of plunging a great one into chaos.

And so there is present the impelling need: the need above all others of finding a scientific, factual approach to man's difficulties, of bringing him to mental health and a mature viewpoint where he will have the power and the desire

To strive, to seek, to find, and not to yield.

THE MASSACHUSETTS CANCER PROGRAM

THE paper by Dr. George L. Parker on the Pondville State Cancer Hospital, which appears elsewhere in this issue of the *Journal*, brings memories to those of us who can say, "All of it I saw, some of it I was."

In gazing at the panorama of twenty years of cancer-control activities, one cannot but feel the absence of those members of the Massachusetts Medical Society who are no longer with us, but whose efforts aided in building the Massachusetts cancer program. Among them may be mentioned: Thomas Almy, George H. Bigelow, Orrin C. Blair, Walter P. Bowers, Martin M. Brown, J. Forrest Burnham, Farrar Cobb, Francis G. Curtis, Robert B. Greenough, Thomas P. Hennelley, William T. Hopkins, Ernest L. Hunt, George A. Leland, Edward D. Leonard, G. Forrest Martin, William J. Pelletier, Charles H. Richardson, Walter Sawyer, Halbert G. Stetson, James S. Stone, Frederick Thompson, William L. Tracy and Philemon E. Truesdale.

To these and to others, the Massachusetts Medical Society, the citizens and the Department of Public Health owe much. The farsightedness, enthusiasm and willingness of these pioneers to devote time and energy to cancer control resulted in a program that has received nation-wide recognition.

In reviewing the accomplishments of the Program one remembers the establishment of the diagnostic clinics; the opening of Pondville Hospital; the inauguration of cured cancer clinics; the survey on cancer and other chronic diseases, followed by the publication of the results in book form; the organization of the co-operative cancer-control committees in every town and city in the Commonwealth, which began in 1935 and extended over a period of years; the teaching clinics for the medical profession; the opening of the cancer wing at Westfield State Sanatorium; the Cancer Manual for Practitioners, sent free to every physician in the Commonwealth; the utilization of the Massachusetts Program for training representatives from other states and countries in cancer control; *The Procedural Analysis of the Compilation of Cancer Data for Statistical Uses in the Massachusetts Department of Public Health Cancer Control Program*, published by the United States Public Health Service and distributed to health departments throughout the United States; the surveys to evaluate cancer education; and the experiment on cancer education in the schools of Lynn and Malden. These activities and others have contributed to make the Massachusetts cancer program the pattern for cancer programs in this country and abroad.

Diagnostic cancer clinics are functioning in eighteen strategic points throughout the Commonwealth. At these clinics, persons with suspected cancer are examined and then returned to their physicians with a statement of whether a malignant tumor was found. In the early years of the program the majority of the patients came as the result of newspaper publicity, but at the present time nearly 90 per cent of them come on the advice of local physicians. Uniform records are kept in all eighteen clinics, and follow-up observation is maintained from the diagnosis of cancer until death. The long-term follow-up study of more than 20,000 patients with cancer is one of the unique features of the program. Of the cancer patients who were seen in 1927, 2 per cent are lost, 11 per cent are still alive, and the remainder are dead.

At the Tumor Diagnosis Laboratory tissue is examined as a free service to any physician in the Commonwealth. The increasing number of specimens submitted by the profession is an indication of the value of this service.

The dissemination of information regarding cancer has been an integral part of the Massachusetts

cancer program. In a nation-wide Gallup Poll held in 1939, only about half the persons interviewed believed that cancer was curable. A few years later, a similar result was found to exist in several Massachusetts cities. Within the past year, professional surveyors visited seven Massachusetts cities, including some of those surveyed earlier, and found that approximately 75 per cent of the people were aware of the curability of cancer. The educational work of the Department of Public Health is done mainly through committees in local communities striving to furnish information through public meetings, distribution of pamphlets, school programs and other means. Recently, the educational program has become a joint effort of the Department of Public Health and the American Cancer Society, Massachusetts Division, Incorporated. These two organizations, working together, should accelerate cancer education.

Throughout the period of the program, statistical studies have been made to measure improvements, to ascertain weaknesses, to evaluate clinic procedures and to determine factors dealing with the etiology of the disease. Among the more recent studies is one to determine the practicability of furnishing the Papanicolaou diagnostic test for vaginal smears to the entire medical profession. This study, financed by the Commonwealth Fund, is now in its third year, and although the study will not be completed for three more years, a few cases have been found in which a positive vaginal smear was the only indication of a uterine cancer. Another important study that has been completed recently deals with the changing cancer death rate, giving consideration to each site separately. Whereas for some years it was noted that there was a downward trend in cancer among women and that this trend occurred in Massachusetts earlier than in other parts of the country, the behavior of the trends for individual sites of cancer have been studied only recently. Even though the general trend of the cancer death rate for women is downward, certain sites, such as the lung, pharynx and ovary, show upward trends. The downward trends for cancer of the skin, mouth, stomach, uterus and perhaps breast are sufficiently great to influence the trend of the total cancer rate for females, but the downward trend for mouth, skin and stomach among males is not sufficiently great to offset the sites with upward trends.

At the Fourth International Cancer Congress, held in St. Louis, the Department of Public Health reported on an interesting finding: about half the women with cancer of the cervix had been married under the age of twenty, contrasted with a rate of about 18 per cent of early marriages in the general population. A large part of the paper was devoted to a discussion of this phenomenon.

The fourth part of the program is hospitalization. This has been so admirably discussed by Dr. Parker that little more need be added, except to decry the fact that many empty beds are to be found in this institution, owing to a lack of personnel. With the great demand of cancer patients and with the present limitation of facilities in general hospitals, it seems deplorable that less than a third of the beds in Pondville are being used. Every effort should be made to assist the superintendent and the staff in their effort to excel the prewar status of this hospital.

SANDERS COLLEGE

THE third postgraduate lecture course, presented by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health in Sanders Theater, Cambridge, completed its annual term on May 5. The statistics here presented well justify the term "Sanders College" that has been applied to the course.

Between March 8 and May 5 ninety-six lectures were given in eighteen sessions. The total registration exceeded 1300, over a hundred more than in 1947; the gross attendance was 7400, with an average of 411 at each session. The sessions on allergy and psychiatry, the least well attended, drew each an audience of approximately 250 "students." A crowd of 850 thronged the sessions on cardiovascular diseases!

Congratulations are due to the Committee on Postgraduate Instruction, which arranged the program, as well as to the Hub of the Universe, where an indifference to learning can hardly be said to have manifested itself.

MEDICOLEGAL ABSTRACT

Liability for Malpractice — Duty of physician to explain cause of injury occurring during treatment. Many doctors have had the experience of a patient dying or being injured under circumstances that according to the ordinary course of events suggest that the doctor was negligent. He may be able to account for his own conduct and feel sure that it was proper even though he cannot explain how the injury occurred. A recent California decision makes it seem prudent for him to do whatever he can to determine the cause of the injury lest he be held responsible.

In an earlier California case (*Ybarra* v. *Spangard*), in which the court, disposing of a contention that a plaintiff could not recover when he failed to show more than that after an appendectomy he had awakened with a painful shoulder, which subsequently resulted in an atrophied and paralyzed arm, stated:

> We merely hold that where a plaintiff received unusual injuries while unconscious and in the course of medical treatment all those defendants who had any control over his body or the instrumentalities which might have caused the injuries may properly be called upon to meet the inference of negligence by giving an explanation of their conduct.

This holding was based upon what is referred to as the doctrine of *Res ipsa loquitur*: that negligence is presumed when a plaintiff is injured by an instrumentality entirely within the defendant's control under circumstances that would not ordinarily arise unless someone had been negligent. The more recent California case clarifies the extent to which the defendants must go in making an explanation of their conduct under such circumstances.

A surgeon planned to remove a wart from a patient's nose after anesthetizing the patient with a nonexplosive gas, and then to remove the tonsils under ether anesthesia. The patient was completely anesthetized with nitrous oxide and oxygen, and the wart was removed with an electric needle. After the surgeon had finished removing the wart and was cauterizing the wound with the electric needle there was a "flash" and a "pop" about 6 inches above the patient's face. As a result of this accident the patient suffered contusions to the left cheek and left eye, bled profusely from the nose and mouth and was hospitalized for fifteen days. The doctor testified that at the time of the "flash" and "pop" the nitrous oxide and oxygen had been turned off and that the ether had not yet been turned on; that to give ether would have required the switching of the apparatus, and that the apparatus had not been switched. The doctor described in detail what he was doing before and at the time of the accident. However, neither the doctor nor the anesthetist could account — and neither attempted to account — for the "flash" and the "pop" that caused the injuries. The director of the anesthetic department of the defendant's hospital was called as a witness by the surgeon. He qualified as an expert on anesthesia, and when asked his opinion as to the cause of the "flash" and the "pop," he made the following statement:

> I think that the strongest possibility. . . . From the information, I suspect. . . . My opinion would be, one probable likelihood would be, from contaminating substance in one of the tanks, some foreign substance.

The nurse in charge of surgery testified that the breathing tube leading from the container to the patient's face had been properly washed with soap and water immediately before its use. The expert on anesthesia admitted that it was possible for a chemical laboratory to test nitrous oxide to determine if it were contaminated. It did not appear whether the defendants had made such a test of the nitrous oxide remaining after the operation. The jury rendered a verdict in favor of all the defendants.

On appeal the plaintiff contended that the jury should have been directed to find for her, and the upper court reversed the judgment and ordered a new trial, saying:

> The showing here goes farther than the establishment of a mere prima facie case under the doctrine of *res ipsa loquitur*. Not only is there a prima facie showing that the accident is one which in the ordinary course of events would not have happened if defendants had used due care but the defendants themselves have established the "possibility" or "probability" that they used an impure and, under the circumstances, dangerous anesthetizing agent. That agent, the nitrous oxide, was at all times concerned in the exclusive possession and control of defendants. If such nitrous oxide was not impure, it was in the power of defendants to prove the fact; if it was impure, as their evidence suggests, then the burden was on them to account for the impurity. The defendants offered to prove neither that the gas was pure nor that they were not responsible for its impurity. We are constrained to the conclusion that in a *res ipsa loquitur* case where, in addition to the prima facie showing of negligence, it is admitted or appears without dispute that the defendant has it in his power to produce substantial evidence material to the issue of negligence but fails to do so, it must be presumed that such evidence, if produced, would have been adverse to defendant, and under such circumstances the evidence is insufficient to support a verdict for the defendant and plaintiff is entitled to a directed verdict.
>
> This is not to say that a defendant in a *res ipsa loquitur* case has the burden of proving himself free from negligence. It is not to say that a defendant must in every such case produce evidence of the actual cause of the accident. It is not to say that the question of the sufficiency of a defendant's explanation — or, if he cannot explain, the sufficiency of his evidence of due care and of impossibility of explanation — is not ordinarily for the jury. The general principle is, as stated by this court in 1919 (in denying a hearing in *Bourguignon* v. *Peninsular Ry. Co.*, 40 Cal. App. 689, 694–695 [181 P. 669]) "that where the accident is of such a character that it speaks for itself, as it did in this case, . . . the defendant will not be held blameless except upon a showing either (1) of a satisfactory explanation of the accident, that is, an affirmative showing of a definite cause for the accident, in which cause no element of negligence on the part of the defendant inheres, or (2) of such care in all possible respects

as necessarily to lead to the conclusion that the accident could not have happened from want of care, but must have been due to some unpreventable cause, although the exact cause is unknown. In the latter case, inasmuch as the process of reasoning is one of exclusion, the care shown must be satisfactory in the sense that it covers all causes which due care on the part of the defendant might have prevented."

The defendants have not met either test above stated. They did not show "a definite cause for the accident" unless it was the use by them of an impure or contaminated anesthetizing agent. Such "definite cause" is not shown to possess "no element of negligence" on their part, although evidence material to this issue was available to them. And in respect to an exclusionary showing, as has been pointed out above, the evidence fails in several respects to support a conclusion "that the accident could not have happened from want of care"; it fails in this regard not because of any showing of impossibility of proof but, rather, because defendants having the ability to produce it chose not to do so. It is therefore apparent that upon any reasonable view of the record, and giving effect to the rules of law hereinabove discussed, the verdict of the defendants cannot be sustained.

In a vigorous dissent by three of the seven justices, it was stated:

> Under the doctrine of *res ipsa loquitur*, the majority opinion in effect imposes upon a defendant even more than the burden of proving that he was not negligent. It imposes the burden of proving the actual cause of the accident, for that is the only practical way under the opinion that defendants can show that they were free from fault. The imposition of such a burden necessarily involves the adoption of a rule on grounds of policy that persons in attendance during an operation must explain not only their own conduct, but the conduct of any other person, such as a manufacturer of anesthetics, who might conceivably be responsible for the accident, as well as the forces of nature that brought it about. Such a rule would impose upon doctors, nurses, and members of hospital staffs absolute liability for unusual accidents that they cannot explain and might discourage their attending operations. A person about to undergo an operation is generally aware that there may be unforeseeable dangers incident thereto. He is entitled to an explanation of the conduct of the persons attending the operation, but he cannot reasonably expect them to be insurers of his safety.

Under the majority opinion the defendants would not have to prove the cause of the injury if they showed that it had not been caused by anything that due care on their part might have prevented. However, it is difficult to determine from the majority opinion in what respect the majority considered the defendant doctors negligent. The court objected to their failure to produce evidence that they might have produced regarding the cause of the injury, but the evidence seemed to refer to possible negligence on the part of the manufacturers of the nitrous oxide or on the part of the hospital in its manner of storing it.

These details of evidence have no direct bearing on other cases involving different facts, but the prudence of determining the actual cause of an injury occurring under circumstances that otherwise suggest negligence on the part of the doctor is plainly indicated. (*Dierman* v. *Providence Hospital, California Advance Reports* 31 A.C. No. 5, January 9, 1948, revising 79 A.C.A. 374.)

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONTAMINATED AMPOULES IN CIRCULATION

A communication has been received from the Federal Food and Drug Administration to the effect that three codes of Obeto Ampuls, manufactured by Ziegler Pharmacal Company, Buffalo, New York, have been found to contain viable yeast or bacteria. The known questionable code numbers are:

7436
7275
7085

Other codes are now being checked.

It is believed that this product has gone directly to physicians. If physicians have in stock any ampoules bearing the three code numbers referred to above, they are requested to return all unused stocks to the manufacturer immediately.

If it is subsequently determined that other codes of this product have been found to be contaminated, physicians will be advised accordingly.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL, 1948

Résumé

Diseases	April 1948	April 1947	Seven-Year Median
Chancroid	0	3	2*
Chicken pox	1971	2667	1751
Diphtheria	18	40	15
Dog bite	1086	1053	1073
Dysentery, bacillary	12	7	2
German measles	130	102	523
Gonorrhea	254	332	332
Granuloma inguinale	0	1	0*
Lymphogranuloma venereum	1	2	3*
Malaria	3	4	4
Measles	5950	1756	4012
Meningitis, meningococcal	2	6	16
Meningitis, Pfeiffer-bacillus	1	7	3
Meningitis, pneumococcal	2	2	6†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	1	1†
Meningitis, other forms	1	1	0†
Meningitis, undetermined	4	2	4†
Mumps	2615	1131	1483
Pneumonia, lobar	114	203	338
Poliomyelitis	0	0	1
Salmonellosis	16	16	6
Scarlet fever	813	486	1422
Syphilis	256	303	419
Tuberculosis, pulmonary	259	261	232
Tuberculosis, other forms	8	17	17
Typhoid fever	3	3	2
Undulant fever	3	5	4
Whooping cough	183	499	568

*Four-year median.

†Six-year median.

Comment

Diseases with incidence above the seven-year median are chicken pox, diphtheria, bacillary dysentery, measles, mumps and salmonellosis.

Diseases with incidence below the seven-year median are German measles, lobar pneumonia, scarlet fever and whooping cough.

Diphtheria has shown a lower incidence six other times during April. Constant effort toward prevention is still needed. Mumps shows the highest incidence for April since 1915. Measles shows the fourth highest April incidence. Whooping cough is at the lowest level for April since 1915.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Athol, 1; Boston, 9; Hanover, 1; Haverhill, 1; Lowell, 1; Natick, 1; Revere, 1; Waltham, 2; Weymouth, 1; total, 18.

Dysentery, bacillary, was reported from: Worcester, 12; total, 12.

Encephalitis, infectious, was reported from: Cambridge, 1; Milton, 1; total, 2.

Malaria was reported from: Boston, 1; Braintree, 1; Malden, 1; total, 3.

Meningitis, meningococcal, was reported from: Dracut, 1; Ware, 1; total, 2.

Meningitis, Pfeiffer-bacillus, was reported from: Rockport, 1; total, 1.

Meningitis, pneumococcal, was reported from: Framingham, 1; Somerville, 1; total, 2.

Meningitis, other forms, was reported from: Quincy, 1; total, 1.

Meningitis, undetermined, was reported from: Haverhill, 1; Melrose, 1; Wakefield, 1; Waltham, 1; total, 4.

Salmonellosis was reported from: Attleboro, 1; Beverly, 2; Boston, 2; Brockton, 1; Holyoke, 2; Lawrence, 1; Millbury, 1; Natick, 2; Peabody, 1; Salem, 2; Worcester, 1; total, 16.

Septic sore throat was reported from: Attleboro, 1; Boston, 4; Brockton, 1; Cambridge, 1; Dartmouth, 1; Greenfield, 1; Medford, 1; Milton, 1; total, 11.

Trichinosis was reported from: Fall River, 1; Hanover, 3; Pembroke, 1; total, 5.

Typhoid fever was reported from: Boston, 2; New Bedford, 1; total, 3.

Undulant fever was reported from: Boston, 1; Weston, 1; Weymouth, 1; total, 3.

MISCELLANY

NEW VETERANS HOSPITAL SITE

Acquisition of a new 15-acre site in Boston for a thousand-bed Veterans Administration general medical and surgical hospital has been approved by President Truman and the Federal Board of Hospitalization.

This tract of land, in Jamaica Plain, is bounded by Heath Street, South Huntington Avenue, Kenney Street and the Jefferson Public School playground.

BLUE SHIELD EXTENSION

The House of Delegates of the Connecticut State Medical Society has voted to establish a prepayment medical-care plan patterned after Blue Shield in Massachusetts.

Medical service plans have also been established recently in Minnesota and in Chicago, and South Carolina has passed an enabling act permitting the formation of a Blue Shield type of prepayment plan in that state.

CORRESPONDENCE

SALT-FREE BREAD

To the Editor: The increasing use of sodium-poor diets for patients with cardiovascular disease raises the problem of finding a baker who will prepare salt-free bread for the use of such patients. I have found Albert Duplain, of 61 Albion Street, Boston, to be most co-operative in making up batches of French-type bread without salt or shortening. No doubt other bakers will show similar willingness to make salt-free bread, although the limited demand will not offer them much financial incentive.

ROBERT W. BUCK, M.D.

5 Bay State Road
Boston 15

NOTICES

ANNOUNCEMENT

Dr. James A. McLaughlin, of Marshfield, announces the opening of an office at 17 Leyden Street, Plymouth, for the practice of internal medicine.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9-10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, June 9 — Further Observations in Hemolytic Anemia. Dr. William Dameshek.

Friday, June 11 — Histochemical Problems in Biology and Medicine. Dr. Edward W. Dempsey.

Wednesday, June 16 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, June 18 — Cardiospasm. Dr. Franz J. Ingelfinger.

Wednesday, June 23 — Myelography. Dr. Samuel Blank.

Friday, June 25 — The Treatment of Migraine. Dr. John R. Graham.

Wednesday, June 30 — Experimental Studies on the Restoration of the Circulation. Dr. Allan D. Callow.

On Tuesday and Thursday mornings from 9 to 10, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On the second and fourth Friday afternoons of each month, therapeutic conferences will be held from 2 to 4 with round-table discussion, Dr. R. P. McCombs, moderator; Dr. Merrill Sosman will conduct x-ray conferences from 4 to 6. On Saturday mornings from 9 to 10 clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12 to 1.

All exercises are open to the medical profession.

NEW ENGLAND PEDIATRIC SOCIETY

The spring meeting of the New England Pediatric Society will be held in New Haven, Connecticut, on Wednesday, June 9.

PROGRAM

At New Haven Hospital (789 Howard Avenue):

12 m. to 1 p.m. Pediatric Conference.
1 to 2 p.m. Luncheon.
2 to 4:30 p.m. Scientific Program.

At New Haven Medical Association (364 Whitney Avenue):

5 to 6 p.m. Social Hour.
6 p.m. Dinner.
7 p.m. Multiple Birth in Colonial Times. Dr. Ernest J. Caulfield, of Hartford, Connecticut.

AMERICAN ASSOCIATION OF MEDICAL MILK COMMISSIONS, INC.

A meeting of the American Association of Medical Milk Commissions, Inc., will be held at the Avalon Hotel, Waukesha, Wisconsin, from June 18 to 21. Dr. Tom D. Spies, of Birmingham, Alabama, will be the principal speaker at the scientific meeting on June 19.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 10

FRIDAY, JUNE 11

*9:00–10:00 a.m. Histochemical Problems in Biology and Medicine. Dr. Edward W. Dempsey. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, JUNE 14

*12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

TUESDAY, JUNE 15

*12:00 m. X-ray Conference. Margaret Jewett Hall Mt Auburn Hospital, Cambridge.

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

(*Notices concluded on page xiii*)